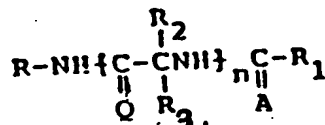


AMINO ACID DERIVATIVE ANTICONVULSANT

1 The present invention relates to compounds and  
pharmaceutical compositions having central nervous system  
(CNS) activity which are useful in the treatment of  
epilepsy and other CNS disorders. More specifically, the  
5 compounds of this invention can be characterized as  
protected amino acid derivatives of the formula:



I

10

or the N-oxides thereof or pharmaceutically acceptable  
salts thereof wherein

R is hydrogen, lower alkyl, lower alkenyl, lower  
alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic  
15 lower alkyl, lower alkyl heterocyclic, lower cycloalkyl,  
lower cycloalkyl lower alkyl, and R is unsubstituted or is  
substituted with at least one electron withdrawing group or  
electron donating group;

R<sub>1</sub> is hydrogen or lower alkyl, lower alkenyl,  
20 lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower  
alkyl, heterocyclic, lower cycloalkyl, lower cycloalkyl  
lower alkyl, each unsubstituted or substituted with an  
electron donating group or an electron withdrawing group  
and

25 R<sub>2</sub> and R<sub>3</sub> are independently hydrogen, lower  
alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl,  
aryl, heterocyclic, heterocyclic lower alkyl, lower alkyl  
heterocyclic, lower cycloalkyl, lower cycloalkyl lower  
alkyl, SO<sub>3</sub><sup>-</sup> or Z-Y wherein R<sub>2</sub> and R<sub>3</sub> may be unsubstituted  
30 or substituted with at least one electron withdrawing group  
or electron donating group;

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1 Z is O, S, S(O)<sub>a</sub>, NR<sub>4</sub>, PR<sub>4</sub> or a chemical bond;  
 Y is hydrogen, lower alkyl, aryl, aryl lower  
 alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic,  
 heterocyclic lower alkyl, cycloalkyl, cycloalkyl lower  
 5 alkyl and Y may be unsubstituted or substituted with an  
 electron donating group or an electron withdrawing group,  
 provided Z is a chemical bond only, when Y is halo, or

ZY taken together is NR<sub>4</sub>NR<sub>5</sub>R<sub>7</sub>, NR<sub>4</sub>OR<sub>5</sub>, ONR<sub>4</sub>R<sub>7</sub>,  
 OPR<sub>4</sub>R<sub>5</sub>, PR<sub>4</sub>OR<sub>5</sub>, SNR<sub>4</sub>R<sub>7</sub>, NR<sub>4</sub>SR<sub>7</sub>, SPR<sub>4</sub>R<sub>5</sub>, PR<sub>4</sub>SR<sub>7</sub>, NR<sub>4</sub>PR<sub>5</sub>R<sub>6</sub>  
 10 PR<sub>4</sub>NR<sub>5</sub>R<sub>7</sub>,  $\begin{array}{c} \text{NR}_4\text{C}-\text{R}_5 \\ \parallel \\ \text{O} \end{array}$ ,  $\begin{array}{c} \text{SCR}_5 \\ \parallel \\ \text{O} \end{array}$ ,  $\begin{array}{c} \text{NR}_4\text{C}-\text{OR}_5 \\ \parallel \\ \text{O} \end{array}$ ,  $\begin{array}{c} \text{SC}-\text{OR}_5 \\ \parallel \\ \text{O} \end{array}$ ,  $\begin{array}{c} \text{NR}_4\text{C}-\text{NR}_5\text{R}_6 \\ \parallel \\ \text{O} \end{array}$ ,

T30X  
 $\begin{array}{c} \text{NR}_4\text{CNR}_5\text{S}(\text{O})_a\text{R}_6 \\ \parallel \\ \text{O} \end{array}$ ,  $\begin{array}{c} \text{NR}_4\text{CNR}_5\text{R}_6 \\ \parallel \\ \text{S} \end{array}$ ,  $\begin{array}{c} \text{NR}_4\text{CMNR}_5\text{COR}_6 \\ \parallel \\ \text{O} \end{array}$ ,  $\begin{array}{c} \text{A} \\ \parallel \\ \text{S} \end{array}$ , or  $\begin{array}{c} \text{C}-\text{NH}_2 \\ \parallel \\ \text{S} \end{array}$

15 R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are independently hydrogen, lower  
 alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower  
 alkynyl, wherein R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> may be unsubstituted or  
 substituted with an electron withdrawing group or an  
 electron donating group and

20 R<sub>7</sub> is R<sub>6</sub> or COOR<sub>8</sub> or COR<sub>8</sub>

R<sub>8</sub> is hydrogen or lower alkyl, or aryl lower  
 alkyl, and the aryl or alkyl group may be unsubstituted or  
 substituted with an electron withdrawing group or an  
 electron donating group and

25 A and Q are independently O or S, M is an  
 alkylene chain containing up to 6 carbon atoms or a  
 chemical bond;

n is 1-4 and

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35

3

a is 1-3.

1           The predominant application of anticonvulsant drugs  
is the control and prevention of seizures associated with  
epilepsy or related central nervous system disorders. Epilepsy  
5           refers to many types of recurrent seizures produced by  
paroxysmal excessive neuronal discharges in the brain; the two  
main generalized seizures are petit mal, which is associated  
with myoclonic jerks, akinetic seizures, transient loss of  
consciousness, but without convulsion; and grand mal which  
10           manifests in a continuous series of seizures and convulsions  
with loss of consciousness.

          The mainstay of treatment for such disorders has been  
the long-term and consistent administration of anticonvulsant  
drugs. Most drugs in use are weak acids that, presumably,  
15           exert their action on neurons, glial cells or both of the  
central nervous system. The majority of these compounds are  
characterized by the presence of at least one amide unit and  
one or more benzene rings that are present as a phenyl group or  
part of a cyclic system.

          Much attention has been focused upon the development  
20           of anticonvulsant drugs and today many such drugs are well  
known. For example, the hydantions, such as phenytoin, are  
useful in the control of generalized seizures and all forms of  
partial seizures. The oxazolidinediones, such as trimethadione  
25           and paramethadione, are used in the treatment of nonconvulsive  
seizures. Phenacemide, a phenylacetylurea, is one of the most  
well known anticonvulsants employed today, while much attention  
has recently been dedicated to the investigation of the  
diazepines and piperazines. For example, U.S. Patent Nos.  
30           4,002,764 and 4,178,378 to Allgeier, et al. disclose esterified  
diazepine derivatives useful in the treatment of epilepsy and  
other nervous disorders. U.S. Patent No. 3,887,543 to  
Nakanishi, et al. describes a thieno [2,3-e][1,4] diazepine

1 compound also having anticonvulsant activity and other  
depressant activity. U.S. Patent No. 4,209,516 to Heckendorn,  
et al. relates to triazole derivatives which exhibit  
5 anticonvulsant activity and are useful in the treatment of  
epilepsy and conditions of tension and agitation. U.S. Patent  
No. 4,372,974 to Fish, et al. discloses a pharmaceutical  
formulation containing an aliphatic amino acid compound in  
which the carboxylic acid and primary amine are separated by  
10 three or four units. Administration of these compounds in an  
acid pH range are useful in the treatment of convulsion,  
disorders and also possess anxiolytic and sedative properties.

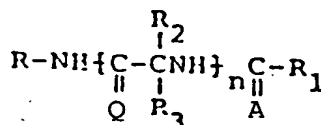
Unfortunately, despite the many available  
pharmacotherapeutic agents, a significant percentage of the  
population with epilepsy or related disorders are poorly  
15 managed. Moreover, none of the drugs presently available are  
capable of achieving total seizure control and most have  
disturbing side-effects. Clearly, current therapy has failed  
to "seize control" of these debilitating diseases.

It is therefore one object of the present invention  
20 to provide novel compounds exhibiting CNS activity,  
particularly anticonvulsant activity.

Another object of this invention is to provide  
pharmaceutical compositions useful in the treatment of epilepsy  
and other CNS disorders.

25 A further object of this invention is to provide a  
method of treating epilepsy and related convulsant disorders.

These and other objects are accomplished herein by  
providing compounds of the following general formula:



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T50X

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1 wherein R, R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, n, Z, Y, A and Q are as defined hereinabove.

5 The present invention contemplates employing the compounds of Formula I in compositions of pharmaceutically acceptable dosage forms. Where the appropriate substituents are employed, the present invention also includes pharmaceutically acceptable addition salts. Moreover, the administration of an effective amount of the present compounds, in their pharmaceutically acceptable forms or the addition salts thereof, can provide an excellent regime for the treatment of epilepsy, nervous anxiety, psychosis, insomnia and other related central nervous disorders.

10 The alkyl groups when used alone or in combination with other groups, are lower alkyl containing from 1 to 6 carbon atoms and may be straight chain or branched. These groups include methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tertiary butyl, amyl, hexyl, and the like.

15 The aryl lower alkyl groups include, for example, benzyl, phenethyl, phenpropyl, phenisopropyl, phenbutyl, and the like, diphenylmethyl, 1,1-diphenylethyl, 1,2-diphenylethyl, and the like.

20 The term aryl, when used alone or in combination, refers to an aromatic group which contains from 6 up to 18 ring carbon atoms and up to a total of 25 carbon atoms and includes the polynuclear aromatics. These aryl groups may be monocyclic, bicyclic, tricyclic or polycyclic and are fused rings. Polynuclear aromatic compound is meant to encompass bicyclic, tricyclic fused aromatic ring system containing from 10-18 ring carbon atoms and up to a total of 25 carbon atoms. The aryl group includes phenyl, and the polynuclear aromatics e.g., naphthyl, anthracenyl, phenanthrenyl, azulenyl and the like. The aryl group also includes groups like ferrocenyl.

1 Lower alkenyl is an alkenyl group containing from 2  
to 6 carbon atoms and at least one double bond. These groups  
may be straight chained or branched and may be in the Z or E  
form. Such groups include vinyl, propenyl, 1-butenyl,  
5 isobutenyl, 2-butenyl, 1-pentenyl, (Z)-2-pentenyl,  
(E)-2-pentenyl, (Z)-4-methyl-2-pentenyl,  
(E)-4-methyl-2-pentenyl, pentadienyl, e.g., 1,3 or 2,4-  
pentadienyl, and the like.

10 The term alkynyl include alkyne substituents  
containing 2 to 6 carbon atoms and may be straight chained as  
well as branched. It includes such groups as ethynyl,  
propynyl, 1-butyne, 2-butyne, 1-pentyne, 2-pentyne,  
3-methyl-1-pentyne, 3-pentyne, 1-hexyne, 2-hexyne,  
3-hexyne and the like.

15 The term cycloalkyl when used alone or in combination  
is a cycloalkyl group containing from 3 to 18 ring carbon atoms  
and up to a total of 25 carbon atoms. The cycloalkyl groups  
may be monocyclic, bicyclic, tricyclic, or polycyclic and the  
rings are fused. The cycloalkyl may be completely saturated or  
20 partially saturated. Examples include cyclopropyl, cyclobutyl,  
cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclodecyl,  
cyclohexenyl, cyclopentenyl, cyclooctenyl, cycloheptenyl,  
decalinyl, hydroindanyl, indanyl, fenchyl, pinenyl, adamantyl,  
and the like. Cycloalkyl includes the cis or trans forms.  
25 Furthermore, the substituents may either be in endo or exo  
positions in the bridged bicyclic systems.

30 The term "electron-withdrawing and electron donating"  
refer to the ability of a substituent to withdraw or donate  
electrons relative to that of hydrogen if the hydrogen atom  
occupied the same position in the molecule. These terms are  
well understood by one skilled in the art and are discussed in  
Advanced Organic Chemistry, by J. March, John Wiley and Sons,  
New York NY, pp. 16-18 (1985) and the discussion therein is

X

1 incorporated herein by reference. Electron withdrawing groups  
include halo, including bromo, fluoro, chloro, iodo and the  
like; nitro, carboxy, lower alkenyl, lower alkynyl, formyl,  
5 carboxyamido, aryl, quaternary ammonium, trifluoromethyl, aryl  
lower alkanoyl, carbalkoxy and the like. Electron donating  
groups include such groups as hydroxy, lower alkoxy, including  
methoxy, ethoxy and the like; lower alkyl, such as methyl,  
ethyl, and the like; amino, lower alkylamino, di(loweralkyl)  
10 amino, aryloxy such as phenoxy, mercapto, lower alkylthio,  
lower alkylmercapto, disulfide (lower alkylthio) and the  
like. One skilled in the art will appreciate that the  
aforesaid substituents may have electron donating or electron  
withdrawing properties under different chemical conditions.  
Moreover, the present invention contemplates any combination of  
substituents selected from the above-identified groups.

15 The term halo includes fluoro, chloro, bromo, iodo  
and the like.

The term acyl includes lower alkanoyl.

20 As employed herein, the heterocyclic substituent  
contains at least one sulfur, nitrogen or oxygen, but also may  
include one or several of said atoms. The heterocyclic  
substituents contemplated by the present invention include  
heteroaromatics and saturated and partially saturated  
heterocyclic compounds. These heterocyclics may be monocyclic,  
bicyclic, tricyclic or polycyclic and are fused rings. They  
25 may contain up to 18 ring atoms and up to a total of 17 ring  
carbon atoms and a total of up to 25 carbon atoms. The  
heterocyclics are also intended to include the so-called  
benzoheterocycles. Representative heterocyclics include furyl,  
thienyl, pyrazolyl, pyrrolyl, imidazolyl, indolyl, thiazolyl,  
30 oxazolyl, isothiazolyl, isoxazolyl, piperidyl, pyrrolinyl,  
piperazinyl, quinolyl, triazolyl, tetrazolyl, isoquinolyl,  
benzofuryl, benzothienyl, morpholinyl, benzoxazolyl,

1 tetrahydrofuryl, pyranlyl, indazolyl, purinyl, indolinyl,  
pyrazolidinyl, imidazolinyl, imadazolidinyl, pyrrolidinyl,  
furazanyl, N-methylindolyl, methylfuryl, pyridazinyl,  
5 pyrimidinyl, pyrazinyl, pyridyl, epoxy, aziridino, oxetanyl,  
azetidiny, the N-oxides of the nitrogen containing  
heterocycles, such as the nitric oxides of pyridyl, pyrazinyl,  
and pyrimidinyl and the like. The preferred heterocyclic are  
thienyl, furyl, pyrroly, benzofuryl, benzothienyl, indolyl,  
methylpyrrolyl, morpholinyl, pyridyl, pyrazinyl, imidazolyl,  
10 pyrimidinyl, pyrazolyl or pyridazinyl. The preferred  
heterocyclic is a 5 or 6-membered heterocyclic compound.  
The especially preferred heterocyclic is furyl, pyridyl,  
pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl,  
oxadiazolyl, epoxy, pyrimidinyl, or pyridazinyl. The most  
15 preferred heterocyclics are furyl, pyrazolyl, pyrrolyl and  
pyridyl. The preferred compounds are those wherein n is 1, but  
di, tri and tetrapeptides are also contemplated to be within  
the scope of the claims.

20 The preferred values of R is aryl lower alkyl,  
especially benzyl, and the preferred  $R_1$  is H or lower alkyl.  
The most preferred  $R_1$  group is methyl.

25 The most preferred electron donating substituent and  
electron withdrawing substituent are halo, nitro, alkanoyl,  
formyl, arylalkanoyl, aryloyl, carboxyl, carbalkoxy,  
carboxamide, cyano, sulfonyl, sulfoxide, heterocyclic,  
guanidine, quaternary ammonium, lower alkenyl, lower alkynyl,  
sulfonium salts, hydroxy, lower alkoxy, lower alkyl, amino,  
lower alkylamino, di(loweralkyl)amino, amino lower alkyl  
30 mercapto, mercaptoalkyl, alkylthio; and alkylldithio. The term  
"sulfide" encompasses mercapto, mercapto alkyl and alkylthio,  
while the term disulfide encompasses alkylldithio. These  
preferred substituents may be substituted on any one of  $R_1$ ,  $R_2$ ,  
 $R_3$ ,  $R_4$ ,  $R_5$  or  $R_6$ ,  $R_7$  or  $R_8$  as defined herein.



1 The ZY groups representative of  $R_2$  and  $R_3$  include  
hydroxy, alkoxy, such as methoxy, ethoxy, aryloxy, such as  
phenoxy; thioalkoxy, such as thiomethoxy, thioethoxy;  
thioaryloxy such as thiophenoxy; amino; alkylamino, such as  
5 methylamino, ethylamino; arylamino, such as anilino; lower  
dialkylamino, such as, dimethylamino; trialkyl ammonium salt,  
hydrazino, alkylhydrazino and arylhydrazino, such as  
N-methylhydrazino, N-phenylhydrazino, carbalkoxy hydrazino,  
aralkoxycarbonyl hydrazino, aryloxycarbonyl hydrazino,  
10 hydroxylamino, such as N-hydroxylamino ( $-NH-OH$ ), lower alkoxy  
amino [ $(NHOR_{18})$  wherein  $R_{18}$  is lower alkyl], N-lower  
alkylhydroxyl amino [ $(NCR_{18})OH$  wherein  $R_{18}$  is lower alkyl],  
N-lower alkyl-O-lower alkyl hydroxyamino, i.e., [ $N(R_{18})OR_{19}$   
wherein  $R_{18}$  and  $R_{19}$  are independently lower alkyl] and  
15 o-hydroxylamino ( $-O-NH_2$ ); alkylamido such as acetamido,  
trifluoroacetamido, lower alkoxyamino, (e.g.  $NH(OCH_3)$ ); and  
heterocyclicamino, such as pyrazoylamino.

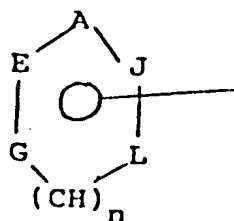
Furthermore, in still another embodiment Z may be  
O, S,  $NR_4$  or  $PR_4$  and Y may be hydrogen, lower alkyl or aryl  
20 and R,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_8$ , n and a are as  
defined hereinabove.

In a still further embodiment, ZY may be  $\overset{\uparrow}{NR_4}CR_5$ ,  
 $\overset{\parallel}{O}$   
or  $\overset{\parallel}{O}SCR_5$  or  $\overset{\parallel}{O}NR_4C-OR_5$ , or  $\overset{\parallel}{O}SC-OR_5$  and  
25

R,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_8$ , n and a are as defined  
hereinabove.

When  $R_2$  or  $R_3$  is heterocyclic, the preferred  
heterocyclics are furyl, tetrahydrofuryl, pyridyl,  
30 pyrazinyl, imidazolyl, pyrazolyl, triazolyl, tetrazolyl,  
oxadiazolyl or epoxy. The most preferred heterocyclic is furyl,  
pyridyl, pyrazoyl and pyrrolyl.

The preferred heterocyclic groups representative of  $R_2$  and  $R_3$  have the formula



XI

or those corresponding partially or fully saturated form thereof wherein  $n$  is 0 or 1

$A$ ,  $Z$ ,  $L$  and  $J$  are independently  $CH$ , or a heteroatom selected from the group consisting of  $N$ ,  $O$ ,  $S$ , and

$G$  is  $CH$ , or a heteroatom selected from the group consisting of  $N$ ,  $O$  and  $S$ ,

but when  $n$  is  $O$ ,  $G$  is  $CH$ , or a heterocyclic selected from the group consisting of  $NH$ ,  $O$  and  $S$  with the proviso that at most two of  $A$ ,  $E$ ,  $L$ ,  $J$  and  $G$  are heteroatoms.

If the ring depicted hereinabove contains a nitrogen ring atom, then the  $N$ -oxide forms are also contemplated to be within the scope of the invention.

When  $R_2$  or  $R_3$  is a heterocyclic of the above formula, it may be bonded to the main chain by a ring carbon atom. When  $n$  is  $O$ ,  $R_2$  or  $R_3$  may additionally be bonded to the main chain by a nitrogen ring atom.

$R_2$  or  $R_3$  may independently also be  $SO_3^-$ , or

Furthermore,  $ZY$  may also be  $\begin{matrix} \text{NR}_4\text{C} \\ \parallel \\ \text{O} \end{matrix} \text{NR}_5\text{R}_6$ ,

$\begin{matrix} \text{NR}_4\text{CNR}_5\text{S(O)aR}_6, \text{NR}_4\text{C-NR}_5\text{R}_6, \text{C} - \text{NH}_2 \text{ or} \\ \parallel \qquad \qquad \parallel \qquad \qquad \parallel \\ \text{O} \qquad \qquad \text{O} \qquad \qquad \text{O} \end{matrix}$

or  $\begin{matrix} \text{R}_4 \text{ CM NR}_5 \text{ C OR}_6. \\ \parallel \qquad \parallel \\ \text{O} \qquad \text{A} \end{matrix}$

1           When R<sub>2</sub> is alkenyl the alkenyl group is a lower  
alkenyl group having 1-6 carbon atoms. The alkenyl group  
may be substituted with an electron donating group and more  
preferably with an electron withdrawing group, such as  
5       COOH.

          As indicated hereinabove, Q and A may be O or S;  
in other words, the main chain may contain only C=O, only  
-C=S or combinations thereof. All such permutations are  
10       contemplated herein. It is preferred that the compounds of  
the present invention contain no more than 2 C=S moieties,  
it is even more preferred that the compounds of the present  
invention contain no more than 1 C=S moiety. The most  
preferred embodiment are when A and Q are both oxygen.

15       An embodiment of the present application is one  
in which the compounds are of Formula I wherein R is lower  
cycloalkyl or lower cycloalkyl lower alkyl, and R is  
unsubstituted or is substituted with at least one electron  
withdrawing group or electron donating group and R<sub>1</sub>, R<sub>2</sub>,  
20       R<sub>3</sub>, Z, Y or ZY taken together, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub>, n and a  
are as defined herein.

          Another embodiment of the present invention  
include compounds of Formula I wherein R<sub>1</sub> is lower  
cycloalkyl or lower cycloalkyl lower alkyl and R<sub>1</sub> may be  
unsubstituted or substituted with an electron donating  
25       group or electron withdrawing group and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, Z, Y,  
or ZY taken together, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub>, R<sub>7</sub>, R<sub>8</sub> n and a are as  
defined hereinabove.

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1 Another embodiment of the present invention  
includes compounds of Formula I wherein  $R_2$  is lower  
cycloalkyl or lower cycloalkyl lower alkyl and  $R_2$  may be  
unsubstituted or substituted with an electron donating  
5 group or electron withdrawing group, and  $R$ ,  $R_1$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  
 $R_6$ ,  $R_7$ ,  $R_8$  and  $a$  are as defined hereinabove.

Still another embodiment of the present invention  
include compounds of Formula I wherein  $R_3$  is lower  
cycloalkyl or lower cycloalkyl lower alkyl and  $R_3$  may be  
unsubstituted or substituted with an electron donating or  
10 electron withdrawing group and  $R$ ,  $R_1$ ,  $R_2$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  
 $R_8$ ,  $n$  and  $a$  are as defined hereinabove.

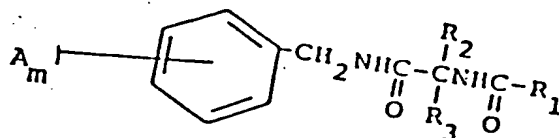
A further embodiment of the present invention  
include compounds of Formula I wherein  $Z$  is  $S(O)_a$  and  $R$ ,  
15  $R_1$ ,  $R_2$ ,  $R_3$ ,  $Y$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $R_7$ ,  $R_8$ ,  $n$  and  $a$  are as defined  
herein.

It is preferred that one of  $R_2$  and  $R_3$  is hydrogen.

In a preferred embodiment, one of  $R_2$  and  $R_3$  is  
hydrogen and that the other is heterocyclic. It is preferred  
20 that one of  $R_2$  and  $R_3$  is a heterocyclic having Formula XI. The  
preferred heterocyclics include furyl, thienyl, benzothienyl,  
benzofuryl, oxazolyl, thiazolyl, isoxazolyl, indolyl,  
pyrazolyl, isoxazolidinyl, benzothienyl, benzofuryl,  
morpholinyl, indolyl, pyrrolyl, furfuryl, and methyl-  
25 pyrrolyl, pyridyl, pyrazinyl, imidazolyl, pyrimidinyl or  
pyridazinyl, pyrazolyl, or epoxy. In another preferred  
embodiment, one of  $R_2$  and  $R_3$  is alkyl (e.g.  
methylisopropyl), aryl (e.g., phenyl), ~~2-thiomethylethyl,~~  
~~lower alkoxy (e.g., phenyl),~~ 2-thiomethylethyl, lower  
30 alkoxy (e.g., ethoxy, methoxy), anilino, propenyl,

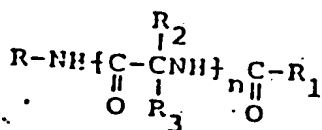
alkylamino (e.g., ethylamino or methylamino). In another preferred embodiment, one of  $R_2$  and  $R_3$  is hydrogen and the other is heterocyclic lower alkyl, lower alkenyl, amino, lower alkoxy amino, N-lower alkylhydroxyamino, lower alkoxyamino, N-lower alkyl-O-lower alkylhydroxyamino or aralkoxycarbonylhydrazino.

Preferred compounds of the present invention have the following general formula:



wherein  $R_1$  is H or lower alkyl,  $R_2$  and  $R_3$  are as defined above and A is hydrogen or an electron donating group or electron-withdrawing group and m is 0-5. It is preferred that A is hydrogen (i.e., m=0). However, values of m equalling 1, 2 or 3 are also preferred.

Preferred embodiments include compounds of Formula I

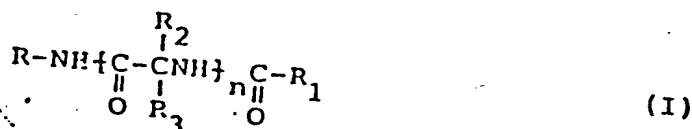


(I)

wherein R and R<sub>1</sub>, independently, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, lower alkyl heterocyclic, each unsubstituted or substituted with at least one substituent;

R<sub>2</sub> and R<sub>3</sub>, independently, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, lower alkyl heterocyclic, each unsubstituted or substituted with at least one substituent; halogen or a heteroatom containing oxygen, nitrogen, sulfur or phosphorous substituted with hydrogen, lower alkyl or aryl, said lower alkyl or aryl groups being substituted or unsubstituted; and n is 1 to 4.

Another preferred embodiment is a compound having Formula I



wherein R is aryl, aryl lower alkyl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic or lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one electron withdrawing substituent or at least one electron donating substituent;

R<sub>1</sub> is H or lower alkyl, unsubstituted or substituted

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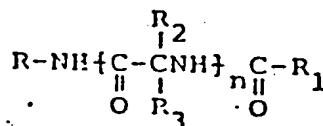
1 with at least one electron withdrawing substituent or at least one electron donating substituent;

5  $R_2$  and  $R_3$ , independently, are hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic, lower alkyl polynuclear aromatic, each unsubstituted or substituted with at least one electron donating substituent, halogen or a heteroatom containing oxygen, nitrogen, sulfur or phosphorous substituted with hydrogen, lower alkyl or aryl, 10 said lower alkyl or aryl groups being substituted or unsubstituted; and

$n$  is 1 to 4.

Another preferred embodiment of the present invention is a compound of Formula I

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wherein  $R$  is aryl lower alkyl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic or lower alkyl polynuclear aromatic, each of which may be unsubstituted or substituted with at least one halo, nitro, acyl, carboxyl, carboalkoxy, carboxamide, cyano, sulfonyl, sulfoxide (sulfinyl), heterocyclic, guanidine, quaternary ammonium hydroxy, alkoxy, 25 alkyl, amino, phenoxy, mercapto, sulfide or disulfide;

25

$R_1$  is H or lower alkyl which may be unsubstituted or substituted with at least one halo, nitro, acyl, carboxamide, cyano, sulfonyl, sulfoxide (sulfinyl), heterocyclic, guanidine, quaternary ammonium, hydroxy, lower alkoxy, amino, phenoxy, 30 sulfide, or disulfide;

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$R_2$  is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, heterocyclic, lower alkyl heterocyclic, polynuclear aromatic, lower alkyl polynuclear aromatic, each

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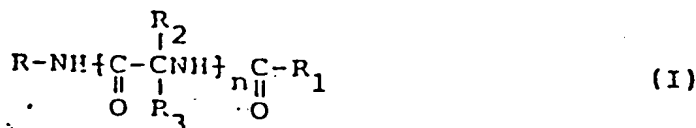
1 unsubstituted or substituted with at least one electron  
withdrawing substituent or at least one electron donating  
substituent; halogen or a heteroatom consisting of oxygen,  
nitrogen, sulfur or phosphorous, said heteroatom being  
5 substituted with hydrogen, lower alkyl or aryl, said lower  
alkyl or aryl groups being substituted or unsubstituted;

$R_3$  is hydrogen, lower alkyl, lower alkenyl, lower  
alkynyl, aryl, heterocyclic, lower alkyl heterocyclic,  
polynuclear aromatic, lower alkyl polynuclear aromatic, each  
10 unsubstituted or substituted with at least one electron  
withdrawing substituent or at least one electron donating  
substituent; halogen or a heteroatom consisting of oxygen,  
nitrogen, sulfur, or phosphorous said heteroatom being  
substituted with hydrogen, lower alkyl or aryl, said lower  
15 alkyl or aryl groups being substituted or unsubstituted;

and  $n$  is 1 to 4;

Another preferred embodiment is a compound of Formula

I



20 wherein R is aryl, aryl lower alkyl, heterocyclic or  
heterocyclic lower alkyl and R is unsubstituted or is  
substituted with at least one electron withdrawing group, or  
electron donating group;

25  $R_1$  is hydrogen or lower alkyl, unsubstituted or  
substituted with an electron donating group or an electron  
withdrawing group and

$R_2$  and  $R_3$  are independently hydrogen, lower alkyl,  
30 lower alkenyl, lower alkynyl, aryl lower alkyl, aryl,  
heterocyclic, heterocyclic lower alkyl, or Z-Y wherein  $R_2$  and  
 $R_3$  may be unsubstituted or substituted with at least one

35

17



electron withdrawing group or electron donating group;

Z is O, S, S(O)<sub>a</sub>, NR<sub>4</sub>, PR<sub>4</sub> or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, heterocyclic, heterocyclic lower alkyl, or halo and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided that when Y is halo, Z is a chemical bond, or

ZY taken together is NR<sub>4</sub>NR<sub>5</sub>R<sub>7</sub>, NR<sub>4</sub>OR<sub>5</sub>, ONR<sub>4</sub>R<sub>7</sub>, OPR<sub>4</sub>R<sub>5</sub>, PR<sub>4</sub>OR<sub>5</sub>, SNR<sub>4</sub>R<sub>7</sub>, NR<sub>4</sub>SR<sub>7</sub>, SPR<sub>4</sub>R<sub>5</sub> or PR<sub>4</sub>SR<sub>7</sub>, NR<sub>4</sub>PR<sub>5</sub>R<sub>6</sub> or

PR<sub>4</sub>NR<sub>5</sub>R<sub>7</sub>, NR<sub>4</sub>CR<sub>5</sub>, SCR<sub>5</sub>, NR<sub>4</sub>COR<sub>5</sub>, SC-OR<sub>5</sub>

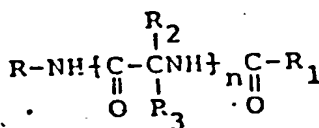
R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> may be unsubstituted or substituted with an electron withdrawing group or an electron donating group and

R<sub>7</sub> is R<sub>6</sub> or COOR<sub>8</sub> or COR<sub>8</sub>, R<sub>8</sub> is hydrogen or lower alkyl, or aryl lower alkyl, wherein the aryl or lower alkyl groups may be unsubstituted or substituted with an electron withdrawing or electron donating group,

n is 1-4 and

a is 1-3.

Another class of preferred compounds of the Formula I have the formula



1 wherein R is aryl, aryl lower alkyl, heterocyclic or  
heterocyclic alkyl which is unsubstituted or substituted with  
at least one electron withdrawing group or at least one  
electron donating group;

5  $R_1$  is hydrogen or lower alkyl which is unsubstituted  
or substituted with at least one electron withdrawing group or  
one electron donating group,

10  $R_2$  and  $R_3$  are independently hydrogen, lower alkenyl,  
lower alkynyl, aryl, aryl lower alkyl, Z-Y or a heterocyclic  
group which may be unsubstituted or substituted with at least  
one electron withdrawing or one electron donating group, with  
the proviso that  $R^2$  and  $R^3$  cannot both be hydrogen;

Z is O, S,  $NR_4$ ,  $PR_4$  or a chemical bond;

15 Y is hydrogen, lower alkyl, aryl, aryl lower alkyl,  
lower alkenyl, lower alkynyl or halo, and Y may be  
unsubstituted or substituted with an electron donating group or  
an electron withdrawing group, provided that when Y is halo, Z  
is a chemical bond; or

20 ZY taken together is  $NR_4NR_5R_6$ ,  $NR_4OR_5$ ,  $ONR_4R_5$ ,  
 $OPR_4R_5$ ,  $PR_4OR_5$ ,  $SNR_4R_5$ ,  $NR_4SR_5$ ,  $SPR_4R_5$ , or  $PR_4SR_5$ ,  $NR_4PR_5R_6$  or  
 $PR_4NR_5R_6$ ,

25  $R_4$ ,  $R_5$  and  $R_6$  are independently hydrogen, lower  
alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl,  
wherein  $R_4$ ,  $R_5$  and  $R_6$  may be unsubstituted or substituted with  
an electron withdrawing group or an electron donating group;

n is 1-4.

Of this preferred group, it is especially preferred that n is  
1.

30 The preferred compounds are those in which R is aryl,  
aryl lower alkyl, heterocyclic, or heterocyclic lower alkyl,  $R_1$   
is hydrogen or lower alkyl,  $R_2$  and  $R_3$  are independently  
hydrogen, heterocyclic, lower alkyl, aryl, lower alkoxy, lower  
alkenyl, amino, hydroxylamino, lower alkoxy amino, N-lower

1 alkyl hydroxyamino, N-lower alkyl-o-lower alkyl hydroxyamino,  
aralkoxy carbonyl hydrazino or alkylmercapto and n is 1.

5 In another preferred embodiment, n is 1, R and R<sub>1</sub> are  
as defined hereinabove and one of R<sub>2</sub> and R<sub>3</sub> is hydrogen and the  
other is heterocyclic, heterocyclic lower alkyl, aryl  
N-hydroxylamino, lower alkoxyamino, N-lower alkylhydroxylamino,  
N-lower alkyl-O-lower alkylhydroxyamino.

10 Another preferred embodiment is wherein n is 1, R and  
R<sub>1</sub> are as defined hereinabove, one of R<sub>2</sub> and R<sub>3</sub> is as defined  
hereinabove or the other is heterocyclic, heterocyclic lower  
alkyl, lower alkyl heterocyclic, aryl, N-hydroxylamino, lower  
alkoxy amino, N-lower alkyl hydroxylamino, N-lower  
15 alkyl-o-lower alkyl hydroxylamino, lower alkoxy, dialkyl lower  
amino, lower alkylamino, aryl lower alkyloxy hydrazino, or  
lower alkylmercapto.

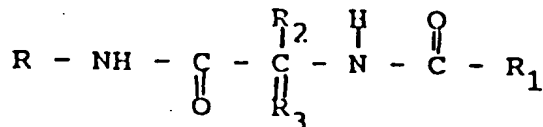
20 The various combination and permutations of the  
Markush groups of R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub> R and n described herein are  
contemplated to be within the scope of the present invention.  
Moreover, the present invention also encompasses compounds and  
compositions which contain one or more elements of each of the  
25 Markush groupings in R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, n and R and the various  
combinations thereof. Thus, for example, the present invention  
contemplates that R<sub>1</sub> may be one or more of the substituents  
listed hereinabove in combination with any and all of the  
substituents of R<sub>2</sub>, R<sub>3</sub> and R with respect to each value of n.

30 The compounds of the present invention may contain  
one (1) or more asymmetric carbons and may exist in racemic and  
optically active forms. The configuration around each  
asymmetric carbon can be in either the D or L form. (It is  
well known in the art that the configuration around a chiral  
35 carbon atoms can also be described as R or S in the  
Cahn-Prelog-Ingold nomenclature system). All of the various  
configurations around each asymmetric carbon, including the

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various enantiomers and diastereomers as well as racemic mixtures and mixtures of enantiomers, diastereomers or both are contemplated by the present invention.

In the principal chain, there exists asymmetry at the carbon atoms to which the groups  $R_2$  and  $R_3$  are attached as substituted. When  $n$  is 1, the compounds of the present invention is of the formula



wherein  $R$ ,  $R_1$ ,  $R_2$ ,  $R_3$ ,  $R_4$ ,  $R_5$ ,  $R_6$ ,  $Z$  and  $Y$  are as defined previously. As used herein, the term configuration shall refer to the configuration around the carbon atom to which  $R_2$  and  $R_3$  are attached, even though other chiral centers may be present in the molecule. Therefore, when referring to a particular configuration, such as D or L, it is to be understood to mean the stereoisomer, including all possible enantiomers and diastereomers. The compounds of the present invention are directed to all of the optical isomers, i.e., the compounds of the present invention are either the L-stereoisomer or the D-stereoisomer. These stereoisomers may be found in mixtures of the L and D stereoisomer, e.g., racemic mixtures. The D stereoisomer is preferred.

Depending upon the substituents, the present compounds may form addition salts as well. All of these forms are contemplated to be within the scope of this invention including mixtures of the stereoisomeric forms.

The following three schemes of preparation are generally exemplary of the process which can be employed for the preparation of the present complex. Although the compounds in the schemes hereinabove contain only the  $\overset{\overset{O}{\parallel}}{C}$  moiety, it is

just as applicable to compounds of

Formula I wherein either A or Q is sulfur or both A or Q are sulfur.

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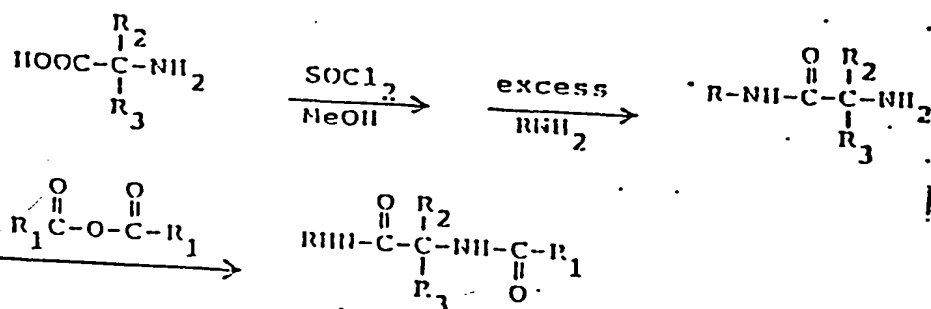
1.

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T220X

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Scheme I

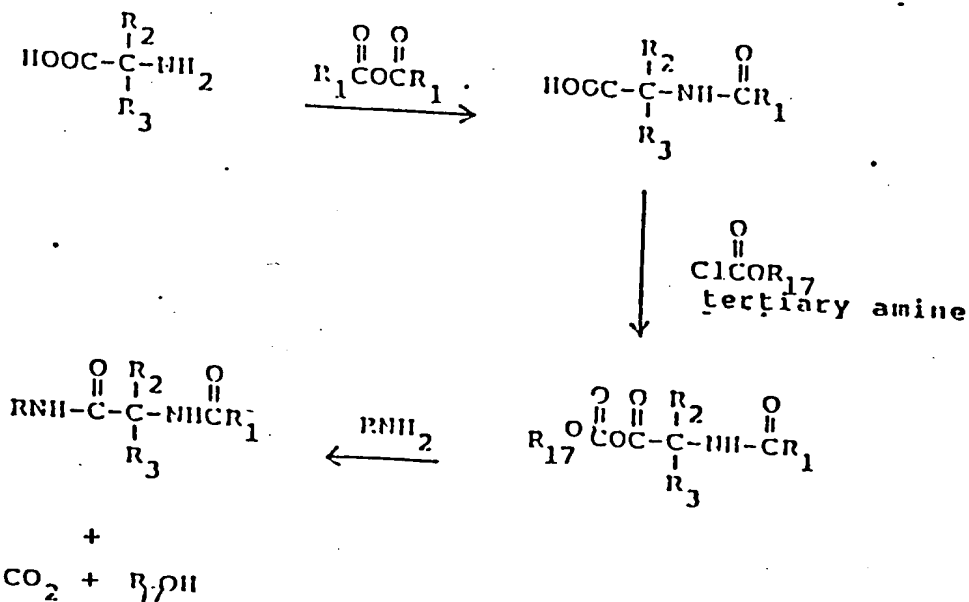


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T221X

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Scheme II



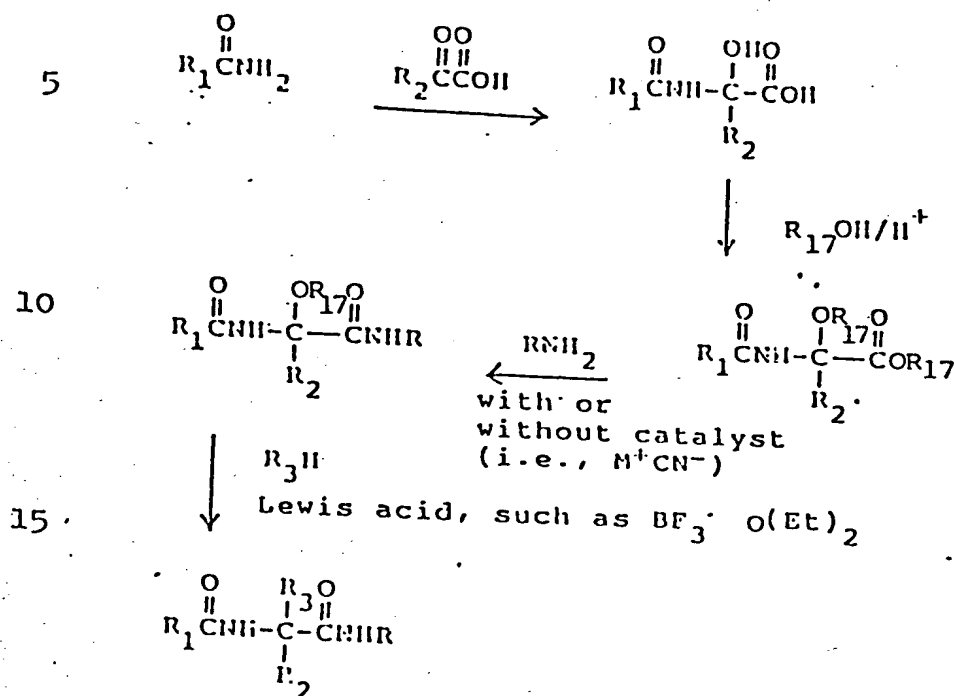
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35 wherein

R<sub>17</sub> = lower alkyl, aryl, aryl lower alkyl,

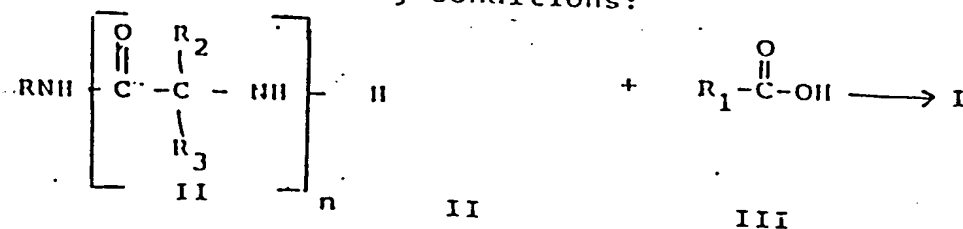
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Scheme III



wherein  $R_3$  = aryl, heteroaromatic and  $R_7$  is as defined hereinabove.

More specifically, these compounds can be prepared by art-recognized procedures from known compounds or readily preparable intermediates. For instance, compounds of Formula I can be prepared by reacting amines of Formula II with an acylating derivative of a carboxylic acid of Formula III under amide forming conditions:



35 wherein  $R$ ,  $R_1$ ,  $R_2$ ,  $R_3$  and are as defined hereinabove and  $n = 1$ .

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The amide forming conditions referred to herein involve the use of known derivatives of the described acids, such as the acyl halides, (e.g.,  $\text{R}_1-\text{C}-\text{X}$ ,

wherein X is Cl, Br and the like), anhydrides

(e.g.,  $\text{R}_1-\text{C}(=\text{O})-\text{O}-\text{C}(=\text{O})-\text{R}_1$ ), mixed anhydrides, lower alkyl esters, carbodiimides, carbonyldiimidazoles, and the like. It is preferred that the acylating derivative used is the

anhydride,  $\text{R}_1-\text{C}(=\text{O})-\text{O}-\text{C}(=\text{O})-\text{R}_1$ . When alkyl esters are employed, amide bond formation can be catalyzed by metal cyanides such as sodium or potassium cyanides.

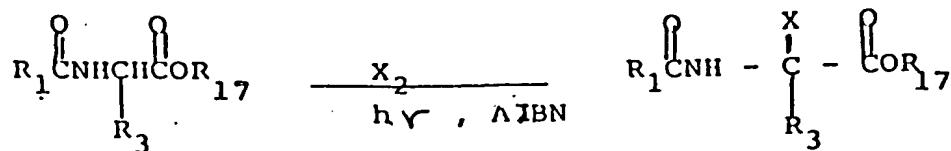
Another exemplary procedure for preparing compounds wherein at least one of  $\text{R}_2$  and  $\text{R}_3$  is aromatic or heteroaromatic is depicted in Scheme IV.

The ester (IV) is reacted with halogen and ultraviolet light in the presence of a catalyst, e.g., AIBN, to form the halo derivative (V). (V) is reacted in the presence of a Lewis acid, such as zinc chloride, with an aromatic or heteroaromatic compound to form the compound (VI). (VI) in turn is hydrolyzed and then reacted with alkylhaloformate, such as alkylchloroformate in the presence of a tertiary amine to generate the mixed N-acyl amino acid carbonic ester anhydride (VIII). This intermediate is reacted with an amine under amide forming conditions to give the compound of Formula I.

Alternatively, (VI) can be reacted directly with an amine ( $\text{RNH}_2$ ) optionally in the presence of a metal catalyst, such as metal cyanides, e.g., potassium or sodium cyanide, under amide forming conditions to form a compound of Formula I.

Alternatively, compound VIII can be prepared by an independent method and converted to VI which is then reacted with an amine, with or without catalyst to form the compound of Formula I.

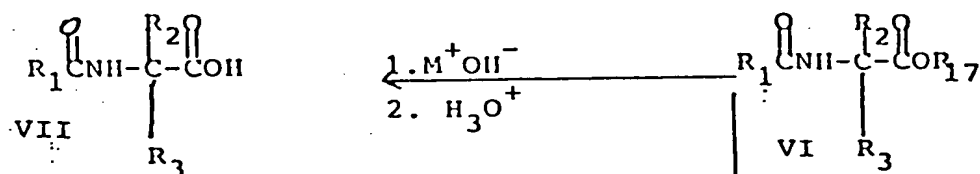
Scheme IV



IV

V

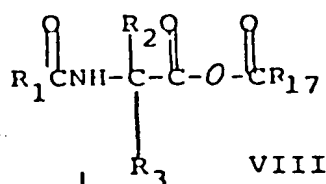
Lewis Acid  
 $\text{R}_2\text{H}$



VII

VI

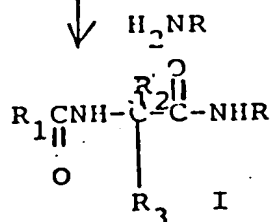
$\text{Cl}-\text{C}(=\text{O})\text{OR}_{17}$   
tertiary amine



VIII

$\text{R NH}_2$

with W  
without catalyst  
(i.e.,  $\text{M}^+\text{CN}^-$ )



I

X = halogen (i.e., Cl, Br)

$\text{R}_{17}$  = lower alkyl, aryl, aryl lower alkyl

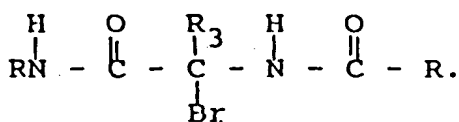
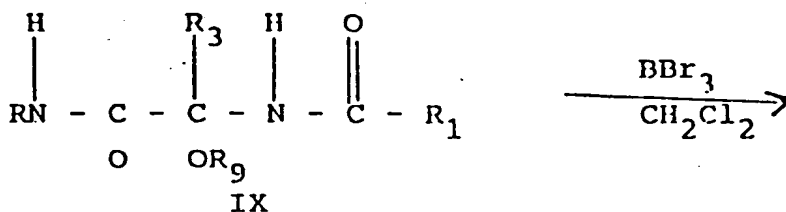
M<sup>+</sup> = metal cation (i.e., Na<sup>+</sup>, K<sup>+</sup>)

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Two additional synthetic routes may be employed for the preparation of compounds wherein  $R_2$  or  $R_3$  is Z-Y as defined hereinabove. In one scheme, for the preparation of these complexes, a substitution reaction is used:

Scheme V



excess  $\text{HR}_2$  or  $\text{MR}_2$   
THF ( $-78^\circ\text{C}$ )

or

compound of Formula I,

1)  $\text{Et}_3\text{N}$

2)  $\text{HR}_2$

THF ( $-78^\circ\text{C}$ )

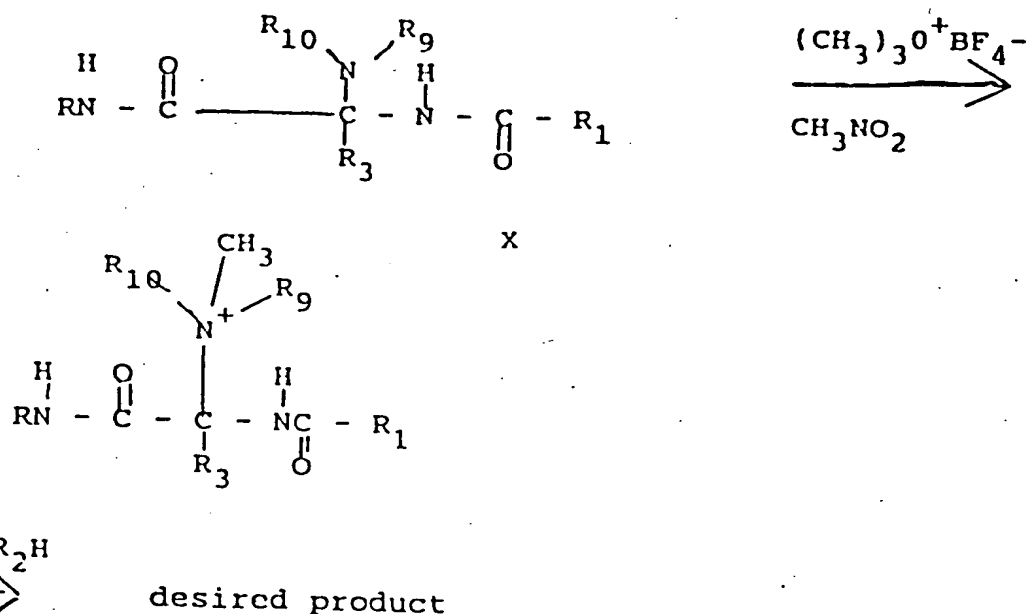
In the above scheme,  $R_9$  is lower alkyl,  $R_2$  is Z-Y and Z, Y, R,  $R_3$  and  $R_1$  are as defined hereinabove.

The ether functionality on IX can be cleaved by treatment with Lewis acids, such as  $\text{BBr}_3$  in an inert solvent such as methylene chloride to form the corresponding halo (bromo) derivative. Addition of either an excess of the  $\text{H-R}_2$  or  $\text{MR}_2$  or the sequential addition of triethylamine and  $\text{H-R}_2$  to a THF mixture containing the halo derivative furnishes the desired product. For example, in the case wherein the compound of Formula IX is 2-acetamido-N-benzyl-2-ethoxy acetamide, its treatment with  $\text{BBr}_3$  in  $\text{CH}_2\text{Cl}_2$  led to the

formation of the  $\alpha$ -bromo derivative, 2-acetamido-N-benzyl-2-bromoacetamide. Addition of an excess of  $\text{HR}_2$  or the sequential addition of  $\text{HR}_2$  to a THF mixture containing the bromo adduct furnishes the desired product.

In another procedure, the product wherein  $\text{R}_2$  or  $\text{R}_3$  is Z-Y can also be prepared by substitution reaction on a quaternary ammonium derivative of the compound of Formula I as outlined below

Scheme VI



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In scheme VI,  $\text{R}$ ,  $\text{R}_1$ ,  $\text{R}_3$  and  $\text{R}$  are as defined hereinabove,  $\text{R}_2$  is Z-Y and  $\text{R}_9$  and  $\text{R}_{10}$  are independently lower alkyl. In scheme VI, methylation of compound X with a methylation reagent, such as trimethyloxonium tetrafluoroborate provided the corresponding ammonium derivative. Subsequent treatment of the ammonium salt with  $\text{HR}_2$  furnishes the desired product. For example, methylation of

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1 2-acetamido-N-benzyl-2-(N,N-dimethylamino) acetamide with  
trimethyloxonium tetrafluoroborate in nitromethane furnished  
the quaternary ammonium derivative,  
2-acetamido-N-benzyl-(N,N,N-trimethylammonium) acetamide  
5 tetrafluoroborate in high yields. Subsequent treatment of the  
salt with the  $HR_2$  reagent in the methanol leads to the  
production of the desired product.

As in any organic reaction, solvents can be employed  
such as methanol, ethanol, propanol, acetone, tetrahydrofuran,  
10 dioxane, dimethylformamide, dichloromethane, chloroform, and  
the like. The reaction is normally effected at or near room  
temperature, although temperatures from 0°C up to the reflux  
temperature of the reaction mixture can be employed.

As a further convenience, the amide forming reaction  
can be effected in the presence of a base, such as tertiary  
15 organic amine, e.g., triethylamine, pyridine,  
4-methylmorpholine, picolines and the like, particularly where  
hydrogen halide is formed by the amide forming reaction, e.g.,  
the reaction acyl halide and the amine of Formula II. Of  
course, in those reactions where hydrogen halide is produced,  
20 any of the commonly used hydrogen halide acceptors can also be  
used.

The exact mineral acid or Lewis acid employed in the  
reaction will vary depending on the given transformation, the  
25 temperature required for the conversion and the sensitivity of  
the reagent toward the acid in the reaction employed.

Compounds of the present invention in which Q or  
A is S are prepared from the corresponding compounds in  
which Q or A is O by art recognized techniques. For  
30 example, one reagent that can be used is Lawesson's reagent,  
i.e., [2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-  
diphosphetane-2-,4-disulfide]. This reagent is a known  
reagent for the thiation of such compounds as ketones,  
carboxamides, esters, lactones, lactams, imides, enamines,  
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A

and S-substituted thioesters. Thus, this reagent can be used to transform compounds of Formula I wherein Q or A is

O to compounds wherein one or both of Q or A is S. The number of  $\text{C}$  groups in the final product is dependent upon

the amount of reagent added and the number of  $\text{C}$  groups

present (i.e., the value of n) in the reactants having Formula I. For example, if n is 1, and both Q and A are oxygen, then the compounds of Formula I have two  $\text{C}$  groups.

Thus, if it is desired that both  $\text{C}$  groups be transformed to

$\text{C}$  then approximately equimolar amount or a slight excess of

is added to compounds of Formula I. On the other hand, if only one  $\text{C}$  group is desired in the final product,

then approximately  $\frac{1}{2}$  molar equivalent of Lawesson's reagent is used.

Furthermore, it is not necessary to add the reagent at the last step of the synthesis; the reagent can be added at any stage of the syntheses outlined in Schemes

I-VI hereinabove. As before, the amount of the reagent

added depends upon the number of  $\text{C}$  desired in the product, and the

number of  $\text{C}$  groups in the reactant.

1 Regardless of which step in the synthesis the reagent is added, the reagent and the compound of Formula I having at least one  $\text{C}=\text{O}$  group or an intermediate thereof is

5 dissolved in an inert solvent, such as THF and heated at a temperature effective to convert the  $\text{C}=\text{O}$  group to a  $\text{C}=\text{S}$ .

10 Temperatures ranging from room temperature to the reflux temperature of the solvent can be used. In cases when  $n = 1$ , it is preferred that the reaction is heated to about reflux if both Q and A are converted to S and that about room temperature be used if one of Q or A is converted to S.

15 The various substituents on the present new compounds, e.g., as defined in R,  $R_1$ ,  $R_2$  and  $R_3$  can be present in the starting compounds, added to any one of the intermediates or added after formation of the final products by the known methods of substitution or conversion reactions. For  
20 example, the nitro groups can be added to the aromatic ring by nitration and the nitro group converted to other groups, such as amino by reduction, and halo by diazotization of the amino group and replacement of the diazo group. Alkanoyl groups can be substituted onto the aryl groups by Friedel-Crafts  
25 acylation. The acyl groups can be then transformed to the corresponding alkyl groups by various methods, including the Woff-Kishner reduction and Clemmenson reduction. Amino groups can be alkylated to form mono, dialkylamino and trialkylamino groups; and mercapto and hydroxy groups can be alkylated to  
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1 form corresponding thioethers or ethers, respectively. Primary  
alcohols can be oxidized by oxidizing agents known in the art  
to form carboxylic acids or aldehydes, and secondary alcohols  
can be oxidized to form ketones. Thus, substitution or  
5 alteration reactions can be employed to provide a variety of  
substituents throughout the molecule of the starting material,  
intermediates, or the final product.

In the above reactions, if the substituents  
themselves are reactive, then the substituents can themselves  
10 be protected according to the techniques known in the art. A  
variety of protecting groups known in the art may be employed.  
Examples of many of these possible groups may be found in  
"Protective Groups in Organic Synthesis," by T.W. Greene, John  
Wiley & Sons, 1981.

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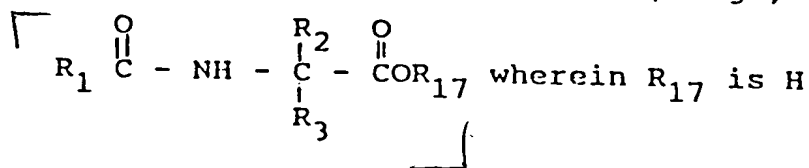
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1 Resulting mixtures of isomers can be separated in the  
pure isomers by methods known to one skilled in the art, e.g.,  
by fractional distillation, crystallization and/or  
chromotagraphy.

5 The present compounds obviously exist in  
stereoisomeric forms and the products obtained thus can be  
mixtures of the isomers, which can be resolved. Optically pure  
functionalized amino acid derivatives can be prepared directly  
from the corresponding pure chiral intermediate. Racemic  
products can likewise be resolved into the optical antipodes,  
10 for example, by separation of diastereomeric salts thereof,  
e.g., by fractional crystallization, by selective enzymatic  
hydrolysis, e.g., papain digestion, or by use of a chiral  
stationary phase in chromatography (HPLC). For a discussion of  
15 chiral stationary phases for HPLC, See, DeCamp, Chirality, 1,  
2-6 (1989), which is incorporated herein by reference with the  
same force and effect as if fully set forth herein.

20 For example, a racemic mixture of any of the  
intermediate in any of the schemes, e.g.,



25 (which can be prepared according to the procedures of Schemes  
1, 2, 3 or 4) is reacted with an optically active amine, RNH<sub>2</sub>,  
e.g., (R)(+)-α-methylbenzylamine to form a pair of  
diastereomeric salts. Diastereomers can then be separated by  
30 recognized techniques known in the art, such as fractional  
recrystallization and the like.

1           In another method, a racemic mixture of final  
products or intermediates can be resolved by using enzymatic  
methods. Since enzymes are chiral molecules, it can be used to  
5       separate the racemic modification, since it will preferentially  
act on one of the compounds, without affecting the enantiomer.  
For example, acylase, such as acylase I, can be used to  
separate the racemic modification of an intermediate  
D,L(+) $\alpha$ -acetamido-2-furanacetic acid. It acts on the L  
10       (+) $\alpha$ -acetamido-2-furanacetic acid, but will not act on the D  
enantiomer. In this way, the D(-) $\alpha$ -acetamido-2-furanacetic  
acid can be isolated. The intermediate can then react with the  
amine ( $\text{RNH}_2$ ) under amide forming conditions as described  
hereinabove to form the compound of Formula I.

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1           The active ingredients of the therapeutic  
compositions and the compounds of the present invention  
exhibit excellent anticonvulsant activity when administered  
in amounts ranging from about 10 mg to about 100 mg per  
5 kilogram of body weight per day. A preferred dosage regimen  
for optimum results would be from about 20 mg to about 50 mg  
per kilogram of body weight per day, and such dosage units  
are employed that a total of from about 1.0 gram to about 3.0  
grams of the active compound for a subject of about 70 kg of  
10 body weight are administered in a 24-hour period. This  
dosage regimen may be adjusted to provide the optimum  
therapeutic response and is preferably administered one to  
three times a day in dosages of about 600 mg per  
administration. For example, several divided doses may be  
15 administered daily or the dose may be proportionally reduced  
as indicated by the exigencies of the therapeutic situation.  
A decided practical advantage is that the active compound may  
be administered in an convenient manner such as by the oral,  
intravenous (where water soluble), intramuscular or  
20 subcutaneous routes.

The active compound may be orally administered, for  
example, with an inert diluent or with an assimilable edible  
carrier, or it may be enclosed in hard or soft shell gelatin  
capsule, or it may be compressed into tablets, or it may be  
25 incorporated directly with the food of the diet. For oral  
therapeutic administration, the active compound may be

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1 incorporated with excipients and used in the form of ingestible  
tablets, buccal tablets, troches, capsules, elixirs,  
5 suspensions, syrups, wafers, and the like. Such compositions  
and preparations should contain at least 1% of active compound.  
The percentage of the compositions and preparations may, of  
course, be varied and may conveniently be between about 5 to  
about 80% of the weight of the unit. The amount of active  
10 compound in such therapeutically useful compositions is such  
that a suitable dosage will be obtained. Preferred  
compositions or preparations according to the present invention  
are prepared so that an oral dosage unit form contains between  
about 5 and 1000mg of active compound.

15 The tablets, troches, pills, capsules and the like  
may also contain the following: A binder such as gum  
tragacanth, acacia, corn starch or gelatin; excipients such as  
dicalcium phosphate; a disintegrating agent such as corn  
starch, potato starch, alginic acid and the like; a lubricant  
such as magnesium stearate; and a sweetening agent such as  
20 sucrose, lactose or saccharin may be added or a flavoring  
agent such as peppermint, oil of wintergreen, or cherry  
flavoring. When the dosage unit form is a capsule, it may  
contain, in addition to materials of the above type, a liquid  
carrier. Various other materials may be present as coatings or  
25 to otherwise modify the physical form of the dosage unit. For  
instance, tablets, pills, or capsules may be coated with  
shellac, sugar or both. A syrup or elixir may contain the  
active compound, sucrose as a sweetening agent, methyl and  
propylparabens as preservatives, a dye and flavoring such as  
30 cherry or orange flavor. Of course, any material used in  
preparing any dosage unit form should be pharmaceutically pure  
and substantially non-toxic in the amounts employed. In  
addition, the active compound may be incorporated into

1 sustained-release preparations and formulations. For example,  
sustained release dosage forms are contemplated wherein the  
active ingredient is bound to an ion exchange resin which,  
optionally, can be coated with a diffusion barrier coating to  
5 modify the release properties of the resin.

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1           The active compound may also be administered  
parenterally or intraperitoneally. Dispersions can also be  
prepared in glycerol, liquid polyethylene glycols, and  
5           mixtures thereof and in oils. Under ordinary conditions of  
storage and use, these preparations contain a preservative to  
prevent the growth of microorganisms.

          The pharmaceutical forms suitable for injectable  
use include sterile aqueous solutions (where water soluble)  
or dispersions and sterile powders for the extemporaneous  
10          preparation of sterile injectable solutions or dispersions.  
In all cases the form must be sterile and must be fluid to  
the extent that easy syringability exists. It must be stable  
under the conditions of manufacture and storage and must be  
preserved against the contaminating action of microorganisms  
15          such as bacteria and fungi. The carrier can be a solvent or  
dispersion medium containing, for example, water, ethanol,  
polyol (for example, glycerol, propylene glycol, and liquid  
polyethylene glycol, and the like), suitable mixtures  
thereof, and vegetable oils. The proper fluidity can be  
20          maintained, for example, by the use of a coating such as  
lecithin; by the maintenance of the required particle size in  
the case of dispersion and by the use of surfactants. The  
prevention of the action of microorganisms can be brought  
about by various antibacterial and antifungal agents, for  
25          example, parabens, chlorobutanol, phenol, sorbic acid,  
thimerosal, and the like. In many cases, it will be  
preferable to include isotonic agents, for example, sugars or  
sodium chloride. Prolonged absorption of the injectable  
compositions can be brought about by the use in the  
30          compositions of agents delaying absorption, for example,  
aluminum monostearate and gelatin.

1 Sterile injectable solutions are prepared by  
incorporating the active compound in the required amount in  
the appropriate solvent with various of the other ingredients  
5 enumerated above, as required, followed by filtered  
sterilization. Generally, dispersions are prepared by  
incorporating the various sterilized active ingredient into a  
sterile vehicle which contains the basic dispersion medium  
and the required other ingredients from those enumerated  
above. In the case of sterile powders for the preparation of  
10 sterile injectable solutions, the preferred methods of  
preparation are vacuum drying and the freeze-drying technique  
which yield a powder of the active ingredient plus any  
additional desired ingredient from previously sterile-  
filtered solution thereof.

15 As used herein, "pharmaceutically acceptable  
carrier" includes any and all solvents, dispersion media,  
coatings, antibacterial and antifungal agents, isotonic and  
absorption delaying agents, and the like. The use of such  
media and agents for pharmaceutical active substances is well  
20 known in the art. Except insofar as any conventional media  
or agent is incompatible with the active ingredient, its use  
in the therapeutic compositions is contemplated.  
Supplementary active ingredients can also be incorporated  
into the compositions.

25 It is especially advantageous to formulate  
parenteral compositions in dosage unit form for ease of  
administration and uniformity of dosage. Dosage unit form as  
used herein refers to physically discrete units suited as  
unitary dosages for the mammalian subjects to be treated;  
30 each unit containing a predetermined quantity of active  
material calculated to produce the desired therapeutic effect  
in association with the required pharmaceutical carrier. The

1 specification for the novel dosage unit forms of the  
invention are dictated by and directly dependent on (a) the  
unique characteristics of the active material and the  
particular therapeutic effect to be achieved, and (b) the  
5 limitations inherent in the art of compounding such an active  
material for the treatment of disease in living subjects  
having a diseased condition in which bodily health is  
impaired as herein disclosed in detail.

10 The principal active ingredient is compounded for  
convenient and effective administration in effective amounts  
with a suitable pharmaceutically acceptable carrier in dosage  
unit form as hereinbefore disclosed. A unit dosage form can,  
for example, contain the principal active compound in amounts  
ranging from about 5 to about 1000 mg, with from about 250 to  
15 about 750 mg being preferred. Expressed in proportions, the  
active compound is generally present in from about 10 to  
about 750 mg/ml of carrier. In the case of compositions  
containing supplementary active ingredients, the dosages are  
determined by reference to the usual dose and manner of  
20 administration of the said ingredients.

25 The compounds of the present invention  
may be administered in combination with other anti-convulsant  
agents, such as phenytoin, phenbarbital, mephentyoin,  
and phenacemide, and the like. This combination  
is likely to exhibit synergistic effects.

30 . For a better understanding of the present invention  
together with other and further objects, reference is made to  
the following description and examples.

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General Methods. Melting points were

determined with a Thomas-Hoover melting point apparatus and are uncorrected. Infrared spectra (IR) were run on a Beckman IR-4250 and Perkin-Elmer 1330 and 283

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spectrophotometers and calibrated against the 1601-cm<sup>-1</sup> band of polystyrene. Absorption values are expressed in wavenumbers (cm<sup>-1</sup>). Proton nuclear magnetic resonance

(<sup>1</sup>H NMR) spectra were recorded on Varian Associates Models T-60 and FT-80A, General Electric QE 300, and

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Nicolet NT-300 NMR spectrometers. Carbon nuclear magnetic resonance (<sup>13</sup>C NMR) spectra were run on a Varian Associates Models FT-80A General Electric QE 300 and Nicolet NT-300 instrument. Chemical shifts are in

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parts per million ( $\delta$  values) relative to Me<sub>4</sub>Si, and coupling constants (J values) are in hertz. Mass spectral data were obtained at an ionizing voltage of 70

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eV on a Hewlett-Packard 5930 gas chromatograph-mass spectrometer and a Bell-Howell 21-491 spectrometer as well as at the Eli Lilly Laboratories on a Varian

NAT-CH-5 spectrometer. High-resolution (EI mode) mass spectra were performed by Drs. James Hudson and John Chinn at the Department of Chemistry, University of

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Texas at Austin, on a CEC21-110B double-focusing magnetic-sector spectrometer at 70eV. Elemental analyses were obtained at Spang Microanalytical Laboratories, Eagle Harbor, MI and at the Eli Lilly Research Laboratories.

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The solvents and reactants were of the best commercial grade available and were used without further purification unless noted. All anhydrous reactions were run under nitrogen, and all glassware was dried before use. In particular, acetonitrile and triethylamine were distilled from CaH<sub>2</sub>, while dichloromethane was distilled from P<sub>2</sub>O<sub>5</sub>. Acetic anhydride, benzaldehyde and ethyl chloroformate were fractionally distilled.

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1 Preparation of N-Acetyl-D- and L-amino acid-N-benzylamides.

5 General Procedure. The D- or L-amino acid amide (11 mmol) was dissolved in dichloromethane (15 mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (18 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane. The following examples 1-7 were prepared according to this procedure.

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EXAMPLE 1

Preparation of N-Acetyl-D,L-alanine-N'-benzylamide.

Acetic anhydride (2.20 g, 0.022 mol) was slowly added to a methylene chloride solution (30 mL) of D,L-alanine-N-benzylamide (3.80 g, 0.021 mol) and allowed to stir at room temperature (3 h). The mixture was then successively washed with H<sub>2</sub>O (15 mL), 1% aqueous NaOH (15 mL) and H<sub>2</sub>O (15 mL), dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated in vacuo. The residue was recrystallized from CH<sub>2</sub>Cl<sub>2</sub>.  
Yield: 2.50 g (54%).

mp 139-141°C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.22 (d, J = 7.1 Hz, 3H), 1.84 (s, 3H), 4.04-4.50 (m, 3H), 7.26 (s, 5H), 8.11 (br d, J = 7.3 Hz, 1H), 8.42 (br t, J = 6 Hz, 1H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>): 18.2, 22.4, 41.9, 48.2, 126.5, 126.9, 128.1, 139.4, 168.9, 172.4 ppm.

IR (CHCl<sub>3</sub>) 3440, 3300, 3005, 1660, 1515 cm<sup>-1</sup>.

Mass spectrum (CI mode), m/e: 221 (P+1); mol wt 220.1208 (Calculated for C<sub>12</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>, 220.1212).

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EXAMPLE 2

N-Acetyl-D-alanine-N'-benzylamide.

Yield: 1.36 g (56%).

mp 139-141°C.

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$[\alpha]_D^{23} = +36.2$  (c 2.5, MeOH).

$^1\text{H}$  NMR (80 MHz, DMSO- $d_6$ ):  $\delta$  1.25 (d, J = 7.1 Hz, 3H), 1.86 (s, 3H), 4.10-4.50 (m, 1H), 4.30 (d, J = 6.0 Hz, 2H), 7.26 (s, 5H), 8.09 (d, J = 7.3 Hz, 1H), 8.40 (t, J = 6.0 Hz, 1H).

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$^{13}\text{C}$  NMR (80 MHz, DMSO- $d_6$ ): 18.3, 22.5, 42.0, 48.4, 126.6, 127.0 (2C), 128.2 (2C), 139.4, 169.2, 172.5 ppm.

IR (KBr): 3290, 1635 (br), 1540, 1455, 700, 695  $\text{cm}^{-1}$ .  
Mass spectrum, m/e (relative intensity): 221 (30), 114 (20), 106 (40), 91 (80), 87 (100), 77 (5), 72 (20), 65 (5).

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Elemental analysis

Calculated for  $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$  65.42% C; 7.34% H; 12.72% N.  
Found 65.31% C; 7.28% H; 12.63% N.

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EXAMPLE 3

N-Acetyl-L-alanine-N'-benzylamide.

Yield: 1.11 g (46%).

mp 139-142°C.

$[\alpha]_D^{23} = -35.3$  (c 2.5, MeOH).

$^1\text{H}$  NMR (80 MHz, DMSO- $d_6$ ):  $\delta$  1.23 (d, J = 7.2 Hz, 3H), 1.86 (s, 3H), 4.26-4.35 (m, 1H), 4.29 (d, J = 5.8 Hz, 2H), 7.22-7.33 (s, 5H), 8.10 (d, J = 7.4 Hz, 1H), 8.42 (t, J = 5.8 Hz, 1H).

$^{13}\text{C}$  NMR (80 MHz, DMSO- $d_6$ ): 18.3, 22.6, 42.0, 48.4, 126.7, 127.0 (2C), 128.3 (2C), 139.5, 169.2, 172.6 ppm.

IR (KBr): 3290, 1635 (br), 1545, 1450, 700, 695  $\text{cm}^{-1}$ .  
Mass spectrum, m/e (relative intensity): 221 (40), 114 (40), 106 (80), 106 (80), 91 (75), 87 (100), 77 (5), 72 (15), 65 (5).

Elemental analysis

Calculated for $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_2$	65.42% C; 7.34% H; 12.72% N.
Found	65.58% C; 7.32% H; 12.43% N.

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EXAMPLE 4

Preparation of N-Acetyl-D,L-phenylglycine-N'-methanamide.

Acetic anhydride (2.90 g, 28 mmol) was added dropwise to D,L-phenylglycine-N-methanamide (3.4 g, 20 mmol) and allowed to stir at room temperature (1.5 h). During this time, a copious white precipitate formed. This material was collected by filtration, dried in vacuo and recrystallized from absolute alcohol.

Yield: 2.00 g (49%).

mp 232-235°C (dec).

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.89 (s, 3H), 2.58 (d,  $J = 4.6$  Hz, 3H), 5.42 (d,  $J = 8.1$  Hz, 1H), 7.35 (s, 5H), 8.18 (br q,  $J = 4.2$  Hz, 1H), 8.47 (d,  $J = 8.1$  Hz, 1H).

$^{13}\text{C}$  NMR (DMSO- $d_6$ ): 22.4, 25.5, 56.3, 127.1, 127.3, 128.1, 139.0, 168.9, 170.3 ppm.

IR (KBr): 3310, 1645  $\text{cm}^{-1}$ .

Mass spectrum (CI mode),  $m/e$ : 207 (P+1).

Elemental analysis

Calculated for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$	64.06% C; 6.86% H; 13.58% N.
Found	63.79% C; 6.66% H; 13.27% N.

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EXAMPLE 5

Preparation of N-Acetylglycine-N-benzylamide.

The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 1.84 g (81%).

mp 140-142°C.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.88 (s, 3H), 3.74 (d,  $J = 5.3$  Hz, 2H), 4.30 (d,  $J = 5.1$  Hz, 2H), 7.27 (s, 5H), 8.37 (br s, 1H), 8.75 (br s, 1H).

$^{13}\text{C}$  NMR (DMSO- $d_6$ ): 22.5, 42.0, 42.5, 126.6, 127.1 (2C), 128.1 (2C), 139.3, 169.0, 169.6 ppm.

IR (KBr): 3060, 1655, 1640, 1560, 1545, 1450, 1300, 740, 710  $\text{cm}^{-1}$ .

Mass spectrum,  $m/e$  (relative intensity): 206 (3), 147 (12), 106 (100), 91 (75), 73 (50).

Elemental analysis

Calculated for $\text{C}_{11}\text{H}_{14}\text{N}_2\text{O}_2$	64.05% C; 6.86% H; 13.58% N.
Found	64.03% C; 6.79% H; 13.61% N.

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EXAMPLE 6

Preparation of N-Acetyl-D,L-valine-N-benzylamide.

The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 2.35 g (86%).

mp 192-193°C.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  0.83 (d, J = 6.7 Hz, 6H), 1.87 (s, 3H), 1.73-2.09 (m, 1H), 4.11 (d, J = 8.8 Hz, 1H), 4.27 (d, J = 5.8 Hz, 2H), 7.26 (s, 5H), 7.89 (d, J = 8.8 Hz, 1H), 8.84 (t, J = 5.8 Hz, 1H).

$^{13}\text{C}$  NMR (DMSO- $d_6$ ): 18.1, 19.2, 22.4, 30.2, 41.9, 57.8, 126.6, 127.1 (2C), 128.1 (2C), 139.4, 169.2, 171.1 ppm.

IR (KBr): 1625, 1540, 1535, 1450, 1380, 1290, 750, 695  $\text{cm}^{-1}$ .

Mass spectrum, m/e (relative intensity): 142 (16), 114 (43), 106 (29), 91 (57), 72 (100).

Elemental analysis

Calculated for  $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2$  67.70% C; 8.13% H; 11.28% N.

Found 67.58% C; 8.05% H; 11.10% N.

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EXAMPLE 7

Preparation of N-Acetyl-D,L-phenylglycine-N-benzylamide.

The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

Yield: 2.05 g (66%).

mp 202-203°C.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.91 (s, 3H), 4.27 (d, J = 5.6 Hz, 2H), 5.50 (d, J = 7.9 Hz, 1H), 7.21 (s, 5H), 7.36 (s, 5H), 8.38-8.86 (m, 2H).

$^{13}\text{C}$  NMR (DMSO- $d_6$ ): 22.3, 42.0, 56.3, 126.6 (2C), 127.0, 127.1 (2C), 127.4 (2C), 128.1 (2C), 138.9, 139.0, 168.9, 169.9 ppm.

IR (KBr): 3020, 1635, 1580, 1540, 1450, 1265, 745, 690  $\text{cm}^{-1}$ .

Mass spectrum, m/e (relative intensity): 283 (20), 264 (21), 149 (100), 131 (20), 118 (34), 106 (92), 91 (70), 79 (56), 77 (54), 65 (45), 51 (37).

Elemental analysis

Calculated for  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$  72.31% C; 6.44% H; 9.92% N.

Found 72.49% C; 6.47% H; 9.89% N.

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1 Preparation of N-Acetyl-D- and L-phenylglycine-N-benzylamide.

5       General Procedure. The chiral Boc-protected  
phenylglycine-N-benzylamide was dissolved in trifluoroacetic  
acid (0.04 M) and was stirred at room temperature (30 min),  
during which time gas evolved. The solution was concentrated  
10 in vacuo and the residue was redissolved in enough methanol  
to form a solution of 0.2 M. Methanesulfonic acid (1 equiv)  
was added dropwise and stirred for 5 min. After  
concentrating the solution in vacuo, the residue was  
repeatedly dissolved in methanol and the solvent was removed  
(3 times). The residue was then dried under vacuum (18 h),  
leaving a yellow oil.

15       Without further purification, the phenylglycine-N-  
benzylamide methanesulfonate was dissolved in tetrahydrofuran  
(0.2 M) and then was cooled in an ice bath. Triethylamine  
(2 equiv) was added dropwise, followed by acetyl chloride  
(1 equiv). The ice bath was removed and stirring was  
continued at room temperature (18 h). The solution was  
concentrated in vacuo and the residue was recrystallized from  
20 1:1 95% ethanol/water. Examples 8 and 9 were prepared  
according to this procedure.

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EXAMPLE 8

N-Acetyl-D-phenylglycine-N-benzylamide.

The reaction was run on an 11.9 mmol scale.

Yield: 2.97 g (88%).

mp 219-221°C.

$[\alpha]_D = -103.0$  (c 1%, EtOH).

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.91 (s, 3H), 4.27 (d, J = 5.5 Hz, 2H), 5.50 (d, J = 7.8 Hz, 1H), 7.14-7.44 (m, 10H), 8.56 (d, J = 7.8 Hz, 1H), 8.79 (t, J = 5.5 Hz, 1H).

$^{13}\text{C}$  NMR (DMSO- $d_6$ ): 22.4, 42.0, 56.4, 126.7, 127.0 (2C), 127.2 (2C), 127.4, 127.9 (2C), 128.1 (2C), 138.9, 139.0, 168.9, 170.0 ppm.

IR (KBr): 3260, 1620, 1525, 1450, 1370, 720, 690  $\text{cm}^{-1}$ .

Mass spectrum, m/e (relative intensity): 203 (2), 149 (94), 106 (100), 91 (32), 86 (43), 77 (14).

Elemental analysis

Calculated for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$	72.32% C; 6.43% H; 9.92% N.
Found	72.04% C; 6.22% H; 9.78% N.

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EXAMPLE 9

N-Acetyl-L-phenylglycine-N-benzylamide.

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Beginning with 16.1 mmol N-t-Boc-L-phenylglycine-N-benzylamide.

Yield: 2.99 g (66%).

mp 221-222°C.

$[\alpha]_D = +105.1$  (c 1%, EtOH).

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$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.99 (s, 3H), 4.36 (d,  $J = 5.6$  Hz, 2H), 5.60 (d,  $J = 8.0$  Hz, 1H), 7.23-7.53 (m, 10H), 8.60 (d,  $J = 8.0$  Hz, 1H), 8.83 (t,  $J = 5.6$  Hz, 1H).

$^{13}\text{C}$  NMR (DMSO- $d_6$ ): 22.4, 42.1, 56.5, 126.8, 127.1 (2C), 127.3 (2C), 127.5, 128.2 (4C), 139.0, 139.1, 169.1, 170.1 ppm.

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IR (KBr): 3295, 1630, 1530, 1450, 1395, 720, 695  $\text{cm}^{-1}$ .

Mass spectrum,  $m/e$  (relative intensity): 223 (1), 203 (2), 149 (98), 106 (100), 91 (32), 86 (43), 77 (11).

Elemental analysis

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Calculated for $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2$	72.32% C; 6.43% H; 9.92% N.
Found	72.53% C; 6.49% H; 9.67% N.

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EXAMPLE 10

Preparation of N-Acetyl-D,L-alanine-N-(3-methoxy)benzylamide.

5 The D,L-amino acid amide (11 mmol) was dissolved in dichloromethane (15mL) and then acetic anhydride (1.23 g, 1.40 mL, 12 mmol) was added dropwise. The solution was stirred at room temperature (4-6 h) and then concentrated to dryness. The residue was recrystallized from chloroform/hexane.

10 Yield: 0.47 g (17%).

mp 112-115°C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.23 (d, J = 7.1 Hz, 3H), 1.85 (s, 3H), 3.73 (s, 3H), 3.99-4.48 (m, 1H), 4.25 (d, J = 6.1 Hz, 2H), 6.58-7.35 (m, 4H), 8.05 (d, J = 7.4 Hz, 1H), 8.35 (t, J = 6.0 Hz, 1H).

15 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>): 18.1, 22.5, 41.8, 48.3, 54.9, 112.2, 112.3, 119.0, 129.2, 141.0, 159.3, 169.0, 172.4 ppm.

IR (KBr): 3270, 3065, 1625, 1580, 1450, 1260, 1150, 1095, 900, 775, 700, 690 cm<sup>-1</sup>.

Elemental analysis

20 Calculated for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>: 62.37% C; 7.26% H; 11.19% N.  
Found 62.29% C; 7.13% H; 11.08% N.

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EXAMPLE 11

Preparation of N-Trimethylacetyl-D,L-alanine-N-benzylamide.

D,L-Alanine-N-benzylamide (3.56 g, 20 mmol) was dissolved in dichloromethane (25 mL) and trimethylacetic anhydride (4.10 g, 4.46 mL, 22 mmol) was added dropwise. The solution was stirred at room temperature (18 h) and then concentrated to dryness. The solid residue was recrystallized from benzene/petroleum ether (30-60°C). Yield: 2.07 g (40%).

mp 123-124°C.

$^1\text{H}$  NMR (DMSO- $d_6$ ):  $\delta$  1.12 (s, 9H), 1.27 (d,  $J = 7.1$  Hz, 3H), 4.23-4.42 (m, 1H), 4.31 (d,  $J = 5.4$  Hz, 2H), 7.23-7.30 (m, 5H), 7.38 (d,  $J = 7.4$  Hz, 1H), 8.26 (t,  $J = 5.4$  Hz, 1H).

$^{13}\text{C}$  NMR (DMSO- $d_6$ ): 18.1, 27.2 (3C), 37.9, 42.0, 48.4, 126.6, 127.0 (2C), 128.2 (2C), 139.4, 172.5, 177.1 ppm.

IR (KBr): 3300, 1630, 1535 (br), 1455, 745, 695  $\text{cm}^{-1}$ .

Mass spectrum,  $m/e$  (relative intensity): 262 (2), 203 (19), 156 (18), 128 (51), 106 (31), 91 (100), 77 (15), 65 (28).

Elemental analysis

Calculated for  $\text{C}_{15}\text{H}_{22}\text{N}_2\text{O}_2$  68.66% C; 8.47% H; 10.68% N.

Found 68.91% C; 8.14% H; 10.61% N.

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EXAMPLE 12

Preparation of N-Acetyl-D,L-methionine-N-benzylamide.

5 N-Acetyl-D,L-methionine (4.78 g, 25 mmol) was combined with acetonitrile (75 mL) and the mixture was placed into an ice/salt water bath (-5°C). Triethylamine (2.53 g, 3.48 mL, 25 mmol) was added dropwise, followed by ethyl chloroformate (2.71 g, 2.39 mL, 25 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0°C. The mixture was then stirred at -5°C (20 min). Benzylamine (3.00 g, 3.06 mL, 28 mmol) in acetonitrile (5 mL) was added dropwise and the mixture was stirred at -5°C (1 h) and then room temperature (18 h).

15 The mixture was filtered and a white precipitate was collected and dried in vacuo and identified as the desired product (<sup>1</sup>H NMR and <sup>13</sup>C NMR analyses). The filtrate was concentrated in vacuo and the residue was combined with hot tetrahydrofuran (50 mL) and cooled in the freezer (3 h), resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo, and identified as triethylammonium hydrochloride.

20 The latter filtrate containing tetrahydrofuran was concentrated in vacuo and the resulting residue was purified by flash column chromatography (ethyl acetate). A white solid ( $R_f = 0.50$ , ethyl acetate) was isolated and was identified as the desired product (<sup>1</sup>H NMR and <sup>13</sup>C NMR analyses). The two solids identified as N-acetyl-D,L-methionine-N-benzylamide were combined and recrystallized from benzene/petroleum ether (30-60°C).

25 Yield: 2.98 g (43%).

30 mp 134-135°C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.69-1.94 (m, 2H), 1.87 (s, 3H), 2.02 (s, 3H), 2.29-2.59 (m, 2H), 4.10-4.53 (m, 1H), 4.29 (d, J = 6.0 Hz, 2H), 7.26 (s, 5H), 8.12 (d, J = 8.5 Hz, 1H), 8.47 (t, J = 6.0 Hz, 1H).

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1  $^{13}\text{C}$  NMR (DMSO- $d_6$ ): 14.6, 22.5, 29.7, 31.8, 42.0, 52.0,  
126.6, 127.0 (2C), 128.2 (2C), 139.4, 169.5, 171.4 ppm.

IR (KBr): 3280, 1630, 1545, 1460, 750, 700  $\text{cm}^{-1}$ .

5 Mass spectrum, m/e (relative intensity): 280 (3), 206 (100),  
164 (29), 146 (20), 106 (54), 91 (76), 77 (14), 65 (24).

Elemental analysis

Calculated for  $\text{C}_{14}\text{H}_{20}\text{N}_2\text{O}_2\text{S}$  59.96% C; 7.20% H; 9.99% N.

Found 60.02% C; 7.14% H; 9.91% N.

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EXAMPLE 13

Preparation of N-Acetylalanine-N'-(3-fluoro)benzylamide.

N-Acetylalanine (3.28 g, 25 mmol) was combined with acetonitrile (100 mL) and the mixture was placed into an ice/salt bath at -5°C. Triethylamine (2.53 g, 3.5 mL, 25 mmol) was added dropwise followed by the addition of ethyl chloroformate (2.71 g, 2.40 mL, 25 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0°C. The mixture was then stirred at -5°C for 20 minutes. 3-Fluorobenzylamine (3.58 g, 28 mmol) and acetonitrile (5 mL) was added dropwise and was stirred at -5°C for one hour and then at room temperature for 18 hours. The reaction became homogenous during this time interval.

The solution was concentrated in vacuo and the residue was combined with hot tetrahydrofuran (100 mL) and cooled in the freezer for 3 hours resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo and identified as triethylammonium hydrochloride (3.51 g, mp 253-257°C). The filtrate was concentrated in vacuo and the resulting yellow solid was recrystallized from chloroform/diethyl ether. Yield: 3.22 g (54%).

mp 120-121°C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>): δ 1.27 (d, J = 7.1 Hz, 3H), 1.90 (s, 3H), 4.23-4.41 (m, 1H), 4.33 (d, J = 6.1 Hz, 2H), 7.05-7.37 (m, 4H), 8.19 (d, J = 7.1 Hz, 1H), 8.53 (t, J = 6.1 Hz, 1H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>): 17.9, 22.4, 41.5, 48.5, 113.3 (d, J = 20.4 Hz), 113.5 (d, J = 21.7 Hz), 122.8, 130.1 (d, J = 7.9 Hz), 142.4 (d, J = 7.4 Hz), 162.3 (d, J = 243.6 Hz), 169.6, 172.8 ppm.

IR (KBr): 3280, 1645, 1545, 1450, 745, 680 cm<sup>-1</sup>.

1 Mass spectrum, m/e (relative intensity): 238 (18), 151 (22),  
124 (49), 114 (47), 109 (100), 87 (76), 72 (27).

Elemental analysis

Calculated

60.48% C; 6.36% H; 11.76% N.

Found

60.55% C; 6.32% H; 11.71% N.

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EXAMPLE 14

Preparation of D,L- $\alpha$ -Acetamido-N-benzyl-3-thiopheneacetamide.

D,L- $\alpha$ -Acetamido-3-thiopheneacetic acid (2.99 g, 15 mmol) was combined with acetonitrile (60 mL) and the mixture was placed into an ice/salt water bath (-5°C). Triethylamine (1.51 g, 2.10 mL, 15 mmol) was added dropwise, followed by ethyl chloroformate (1.63 g, 1.43 mL, 15 mmol). All additions were done slowly so that the temperature of the mixture did not rise above 0°C. The mixture was then stirred at -5°C (20 min). Benzylamine (1.77 g, 1.80 mL, 16.5 mmol) in acetonitrile (10 mL) was added dropwise and the mixture was stirred at -5°C (1 h) and then room temperature (18 h). The mixture was concentrated in vacuo and the residue was combined with hot tetrahydrofuran (50 mL) and cooled in the freezer (3 h), resulting in the formation of a white precipitate. The mixture was filtered and the precipitate was collected, dried in vacuo, and identified as triethylammonium hydrochloride (<sup>1</sup>H NMR analysis). The filtrate was concentrated in vacuo and the resulting yellow solid was recrystallized from 1:1 95% ethanol/water. Yield: 1.91 g (44%).

mp 198-199°C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.91 (s, 3H), 4.29 (d, J = 5.2 Hz, 2H), 5.61 (d, J = 7.9 Hz, 1H), 7.15-7.50 (m, 3H), 8.55 (d, J = 7.9 Hz, 1H), 8.74 (t, J = 5.2 Hz, 1H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>): 22.3, 42.0, 52.5, 122.4, 126.1, 126.7, 127.0 (3C), 128.2 (2C), 139.0, 139.2, 169.0, 169.8 ppm.

IR (KBr): 3460, 1675, 1570, 1400, 720, 695 cm<sup>-1</sup>.

Mass spectrum, m/e (relative intensity): 288 (2), 245 (3), 155 (88), 112 (100), 91 (31), 85 (17), 65 (7).

Elemental analysis

Calculated for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S 62.48% C; 5.59% H; 9.71% N.  
Found 62.41% C; 5.47% H; 9.55% N.

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EXAMPLE 15

Preparation of D,L- $\alpha$ -Acetamido-N-benzyl-2-thiopheneacetamide

5 N-Acetyl-D,L-ethoxyglycine-N-benzylamide (6.26 g, 25 mmol) was combined with dry ether (175 mL) and then boron trifluoride etherate (5.68 g, 5.0 mL, 40 mmol) was added dropwise, resulting in a homogeneous solution. After stirring a short time, a small amount of a yellow oil separated from the solution. Thiophene (8.41 g, 8.0 mL, 100 mmol) was then added dropwise via syringe and the reaction was stirred at room temperature (4 d). The mixture was cooled in an ice bath and cold aqueous saturated NaHCO<sub>3</sub> (200 mL) was added and the aqueous layer was extracted with ethyl acetate (2 x 100 mL). The organic washings and the original ether layer were combined, dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was purified by flash column chromatography, using 94:6 chloroform/methanol as an eluant (R<sub>f</sub> = 0.7 94:6 chloroform/methanol), and then recrystallized from benzene.

20 Yield: 2.67 g (37%).

mp 167-169°C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>):  $\delta$  1.91 (s, 3H), 4.31 (d, J = 6.0 Hz, 2H), 5.74 (d, J = 7.9 Hz, 1H), 6.99-7.44 (m, 8H), 8.64 (d, J = 7.9 Hz, 1H), 8.85 (t, J = 6.0 Hz, 1H).

25 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>): 22.4, 42.3, 52.2, 125.6, 125.8, 126.6, 126.9, 127.3 (2C), 128.3 (2C), 139.0, 141.4, 169.2, 169.3 ppm.

Mass spectrum, m/e (relative intensity): 289 (2), 181 (6), 155 (100), 112 (100), 91 (100), 85 (34), 74 (24).

30 Elemental analysis

Calculated for C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S 62.48% C; 5.59% H; 9.71% N.  
Found 62.64% C; 5.73% H; 9.61% N.

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EXAMPLE 16

Preparation of D,L- $\alpha$ -Acetamido-N-benzyl-2-furanacetamide.

N-Acetyl-D,L-2-(2-furyl)glycine (0.47 g, 2.56 mmol) was combined with acetonitrile (10 mL) and cooled to -5°C (ice/salt water bath). Triethylamine (0.26 g, 0.36 mL, 2.56 mmol) was then rapidly added and the mixture stirred at -5°C (3 min). Ethyl chloroformate (0.28 g, 0.25 mL, 2.56 mmol) was added dropwise between -4°C and -3°C, and the resulting suspension was stirred at -4°C (20 min), and then an acetonitrile solution (2 mL) of benzylamine (0.30 g, 0.31 mL, 2.82 mmol) was carefully added. During the addition of benzylamine the temperature of the solution did not go above 0°C. The mixture was stirred at -5°C (1 h) and at room temperature (18 h), and then concentrated in vacuo. The residue was then triturated with hot tetrahydrofuran (5 mL), cooled at -16°C (3 h), and the resulting white precipitate was filtered and identified as triethylamine hydrochloride (<sup>1</sup>H NMR, 60 MHz,  $\delta$  1.00 (t, J = 7.5 Hz, CH<sub>3</sub>), 2.82 (q, J = 7.5 Hz, CH<sub>2</sub>), 3.83 (s, NH)). The filtrate was evaporated to dryness in vacuo and the resulting oil purified by flash chromatography (98:2 chloroform/methanol) to give 0.09 g (13%) of the desired product as a white solid: R<sub>f</sub> 0.30 (98:2 chloroform/methanol). mp 178-179°C.

<sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>):  $\delta$  1.90 (s, CH<sub>3</sub>), 4.31 (d, J = 6.0 Hz, CH<sub>2</sub>), 5.58 (d, J = 8.1 Hz, CH), 6.27-6.33 (m, C<sub>3</sub>-H), 6.40-6.44 (m, C<sub>4</sub>-H), 7.20-7.36 (m, Ph), 7.60-7.64 (m, C<sub>5</sub>-H), 8.57 (d, J = 8.1 Hz, NH), 8.73 (t, J = 6.0 Hz, NH).  
<sup>13</sup>C NMR (300 MHz, DMSO-d<sub>6</sub>): 22.35 (CH<sub>3</sub>), 42.27 (CH<sub>2</sub>), 50.95 (CH), 107.60 (C<sub>3</sub>), 110.55 (C<sub>4</sub>), 126.82 (2C<sub>2</sub> or 2C<sub>3</sub>), 127.08 (2C<sub>2</sub> or 2C<sub>3</sub>), 128.27 (C<sub>4</sub>), 139.05 (C<sub>1</sub>), 142.58 (C<sub>5</sub>), 151.16 (C<sub>2</sub>), 168.02 (CH<sub>3</sub>CO), 169.30 (NHCO) ppm.

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1 IR (KBr): 3230, 1625 (br), 1525 (br), 1375 (br), 1230, 1090,  
890  $\text{cm}^{-1}$ .

Mass spectrum, m/e (relative intensity): 273 (1), 139 (100),  
96 (94), 91 (51), 65 (9).

5 Elemental analysis

Calculated for  $\text{C}_{15}\text{H}_{16}\text{N}_2\text{O}_3$

Found

66.16% C; 5.83% H; 10.29% N.

65.92% C; 5.83% H; 10.15% N.

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EXAMPLE 17

Preparation of D,L-  $\alpha$ -Acetamido-N-benzyl-2-pyrroleacetamide.

2-Acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) was suspended in anhydrous ethyl ether (60 mL), and then boron trifluoride etherate (1.82 g, 1.57 mL, 12.8 mmol) was added in one portion and the resulting solution was stirred (15 min). The pyrrole (2.14 g, 2.22 mL, 32 mmol) was then added in one portion and the solution was stirred at room temperature (48 h) during which time a precipitate formed. Hexanes (80 mL) were then added to the suspension, and the mixture was filtered and the brown semi-solid was triturated with 95:5 chloroform/methanol (30 mL) to furnish a green solid. This material was purified by flash chromatography (95:5 chloroform/methanol) to yield 0.94 g (35%) of the desired product as a white solid:  $R_f$  0.29 (96:4 chloroform/methanol).  
mp 174-175°C.

$^1H$  NMR (300 MHz,  $CD_3CN$ ):  $\delta$  1.93 (s,  $CH_3$ ), 4.35 (d,  $J = 6.0$  Hz,  $CH_2$ ), 5.42 (d,  $J = 6.9$  Hz, CH), 6.00-6.18 (m,  $C_3^*H$ ,  $C_4^*H$ ), 6.68-6.72 (m,  $C_5^*H$ ), 7.04 (d,  $J = 6.9$  Hz, NH), 7.17 (t,  $J = 6.0$  Hz, NH), 7.10-7.47 (m, Ph), 9.10-9.80 (br s, NH).

$^{13}C$  NMR (300 MHz,  $CD_3CN$ ): 23.02 ( $CH_3$ ), 43.83 ( $CH_2$ ), 52.65 (CH), 107.57 ( $C_3^*$ ), 108.85 ( $C_4^*$ ), 119.33 ( $C_5^*$ ), 127.96 ( $C_2^*$ ), 128.01 ( $2C_2^{**}$  or  $2C_3^{**}$ ), 128.09 ( $2C_2^{**}$  or  $2C_3^{**}$ ), 129.49 ( $C_4^{**}$ ), 140.01 ( $C_1^{**}$ ), 170.94 ( $COCH_3$ ), 171.21 (CONH) ppm.

IR (KBr): 3320, 1570 (br), 1470 (br), 1330, 1230, 950, 890, 860, 760, 710, 690, 655  $cm^{-1}$ .

Mass spectrum, m/e (relative intensity): 171 (12), 228 (2), 213 (1), 180 (2), 164 (9), 137 (93), 108 (20), 95 (100), 91 (38), 82 (35), 68 (15).

High resolution mass spectral analysis

Calculated for  $C_{15}H_{17}N_3O_2$  271.13208.

Found 271.13144.

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EXAMPLE 18

Preparation of D,L-2-Acetamido-N-benzyl-2-ethoxyacetamide.

An ethanolic solution (420 mL) of ethyl 2-acetamido-2-ethoxyacetate (27.92 g, 147 mmol) and benzylamine (23.70 g, 24 mL, 221 mmol) was stirred at 40-45°C for 3 days. The reaction mixture was evaporated in vacuo and the residue recrystallized (1:3.5 tetrahydrofuran/hexanes (650 mL)) to yield 25.80 g (70%) of the desired product as beige crystals:  $R_f$  0.59 (95:5 chloroform/methanol). mp 153-155°C.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  1.20 (t,  $J = 7.0$  Hz,  $\text{CH}_3$ ), 2.07 (s,  $\text{CH}_3$ ), 3.60-3.76 (m,  $\text{CH}_2\text{CH}_3$ ), 4.40-4.54 (m,  $\text{CH}_2\text{NH}$ ), 5.60 (d,  $J = 8.7$  Hz, CH), 6.63 (d,  $J = 8.7$  Hz, NH), 7.00 (br s, NH), 7.26-7.36 (m, Ph).

$^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ ): 15.06 ( $\text{CH}_3\text{CH}_2$ ), 23.25 ( $\text{CH}_3\text{CO}$ ), 43.60 ( $\text{CH}_2\text{NH}$ ), 64.51 ( $\text{CH}_2\text{CH}_3$ ), 77.43 (CH), 127.69 ( $2\text{C}_2$  or  $2\text{C}_3$ ,  $\text{C}_4$ ), 128.79 ( $2\text{C}_2$  or  $2\text{C}_3$ ), 137.57 ( $\text{C}_1$ ), 168.13 ( $\text{COCH}_3$ ), 171.29 (CONH) ppm.

IR (KBr): 3260, 1630 (br), 1550 (sh), 1505 (br), 1380, 1360, 1230, 1115, 1060, 1015, 890, 745, 690  $\text{cm}^{-1}$ .

Mass spectrum, m/e (relative intensity): 251 (4), 163 (9), 116 (98), 106 (34), 91 (98), 74 (100).

Elemental analysis

Calculated for $\text{C}_{13}\text{H}_{16}\text{N}_2\text{O}_3$	62.38% C; 7.25% H; 11.19% N.
Found	62.49% C; 7.27% H; 11.24% N.

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EXAMPLE 19

Preparation of D,L-2-Acetamido-N-benzyl-2-methoxyacetamide.

To a methanolic solution (180 mL) of methyl 2-acetamido-2-methoxyacetate (8.73 g, 54 mmol) was rapidly added benzylamine (8.68 g, 8.80 mL, 81 mmol) and then the mixture was stirred at 50°C (3 days) during which time a beige precipitate appeared. The solvent was removed in vacuo and the resulting precipitate was recrystallized from tetrahydrofuran (2x) to give 7.67 g (32%) of the desired product as beige crystals:  $R_f$  0.35 (95:5 chloroform/methanol). mp 145-146°C.

$^1\text{H}$  NMR (300 MHz,  $\text{CDCl}_3$ ):  $\delta$  2.06 (s,  $\text{CH}_3\text{CO}$ ), 3.37 (s,  $\text{CH}_3\text{O}$ ), 4.40-4.35 (m,  $\text{CH}_2$ ), 5.52 (d,  $J = 8.7$  Hz, CH), 7.12 (d,  $J = 8.7$  Hz, NH), 7.20-7.40 (m, Ph, NH).

$^{13}\text{C}$  NMR (300 MHz,  $\text{CDCl}_3$ ): 23.03 ( $\text{CH}_3\text{CO}$ ), 43.51 ( $\text{CH}_2$ ), 55.84 ( $\text{CH}_3\text{O}$ ), 78.94 (CH), 127.62 ( $\text{C}_4$ ), 127.70 ( $2\text{C}_2$  or  $2\text{C}_3$ ), 128.70 ( $2\text{C}_2$  or  $2\text{C}_3$ ), 137.45 ( $\text{C}_1$ ), 166.91 ( $\text{COCH}_3$ ), 171.57 (CONH) ppm.

IR (KBr): 1260, 1825 (br), 1550, 1505, 1435, 1390, 1370, 1230, 1120, 1050, 935, 890, 690  $\text{cm}^{-1}$ .

Mass spectrum, m/e (relative intensity): 237 (1), 205 (2), 177 (2), 163 (4), 146 (1), 134 (1), 121 (2), 106 (26), 102 (98), 91 (95), 77 (13), 61 (100).

Elemental analysis

Calculated for  $\text{C}_{12}\text{H}_{16}\text{N}_2\text{O}_3$  61.00% C; 6.83% H; 11.86% N.  
60.91% C; 6.85% H; 11.66% N.

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EXAMPLE 20

Preparation of (D,L)- $\alpha$ -Acetamido-N-benzyl-2-(5-methylfuran)acetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (2.00 g, 8.0 mmol) was suspended in anhydrous ethyl ether, and then boron trifluoride etherate (1.82 g, 12.8 mmol) was rapidly added, and the resulting solution was stirred for 15 min. The 2-methylfuran (2.63 g, 32.0 mmol) was then added and the reaction was stirred at room temperature (3 d). The reaction mixture was poured into an aqueous saturated  $\text{NaHCO}_3$  solution and extracted with ethyl acetate (3 x). The ethyl acetate extracts were combined, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated *in vacuo* to give a beige solid, which was purified by flash chromatography (98:2 chloroform/methanol) to give the desired product as a white crystalline solid.

Yield: 1.40 g (61%)

$R_f$  0.25 (98:2 chloroform/methanol).

mp 148-150 °C.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.88 (s,  $\text{CH}_3\text{CO}$ ), 2.23 (s,  $\text{CH}_3$ ), 4.24-4.36 (m,  $\text{CH}_2$ ), 5.49 (d,  $J = 8.0$  Hz,  $\text{CH}$ ), 6.01 (br s,  $\text{C}_3\text{H}$ ), 6.14 (d,  $J = 2.4$  Hz,  $\text{C}_4\text{H}$ ), 7.20-7.31 (m, Ph), 8.52 (d,  $J = 8.0$  Hz,  $\text{NH}$ ), 8.69 (t,  $J = 5.6$  Hz,  $\text{NH}$ ).

$^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ) 13.44 ( $\text{CH}_3$ ), 22.35 ( $\text{CH}_3\text{CO}$ ), 44.11 ( $\text{CH}_2$ ), 53.23 ( $\text{CH}$ ), 107.51 ( $\text{C}_3'$  or  $\text{C}_4'$ ), 110.40 ( $\text{C}_3'$  or  $\text{C}_4'$ ), 128.13 ( $\text{C}_4''$ ), 128.18 ( $2\text{C}_2''$  or  $2\text{C}_3''$ ), 129.43 ( $2\text{C}_2''$  or  $2\text{C}_3''$ ), 139.69 ( $\text{C}_1''$ ), 149.18 ( $\text{C}_2'$  or  $\text{C}_5'$ ), 153.81 ( $\text{C}_2'$  or  $\text{C}_5'$ ), 170.78 ( $\text{CH}_3\text{CO}$ ), 173.03 ( $\text{CONH}$ ) ppm.

IR (KBr) 3270, 1620 (br), 1520 (br), 1440, 1360, 1210, 1010  $\text{cm}^{-1}$ .

Mass spectrum,  $m/e$  (relative intensity) 286 (3), 179(8), 153 (57), 152 (57), 111 (23), 110 (100), 97 (23), 91 (31).

Elemental Analysis

Calculated: 67.12% C; 6.34% H; 9.78% N.

Found: 66.92% C; 6.52% H; 9.52% N.



EXAMPLE 21

Preparation of (D,L)- $\alpha$ -Acetamido-N-benzyl-2-benzofuranacetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (1.00 g, 4 mmol) was suspended in anhydrous ethyl ether (30 mL) and then boron trifluoride etherate (0.91 g, 6.3 mmol) was rapidly added, and the resulting solution was stirred for 15 min. The benzofuran (1.89 g, 16 mmol) was then added and the reaction was stirred at room temperature (3 d). The reaction mixture was poured into an ice-cold saturated aqueous solution of  $\text{NaHCO}_3$ , and then the mixture was maintained at this temperature for an additional 15 min. The mixture was extracted with ethyl acetate (2 x), and the organic layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated in vacuo. The residue was purified by flash chromatography (100% chloroform, then 99:1 chloroform/methanol) to yield the desired product.

Yield: 0.43 g (33%).

$R_f$  0.30 (98:2 chloroform/methanol).

mp 195-196 °C;

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.94 (s,  $\text{CH}_3\text{CO}$ ), 4.34 (d,  $J = 5.7$  Hz,  $\text{CH}_2$ ), 5.77 (d,  $J = 8.1$  Hz,  $\text{CH}$ ), 7.24-7.32 (m,  $\text{C}_3\text{-H}$ ,  $\text{C}_5\text{-H}$ ,  $\text{C}_6\text{-H}$ , Ph), 7.54 (d,  $J = 7.0$  Hz,  $\text{C}_4\text{-H}$  or  $\text{C}_7\text{-H}$ ), 7.62 (d,  $J = 7.0$  Hz,  $\text{C}_4\text{-H}$  or  $\text{C}_7\text{-H}$ ), 8.74 (d,  $J = 8.1$  Hz,  $\text{NH}$ ), 8.86 (t,  $J = 5.7$  Hz,  $\text{NH}$ ).

$^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ) 22.27 ( $\text{CH}_3\text{CO}$ ), 42.30 ( $\text{CH}_2$ ), 51.22 ( $\text{CH}$ ), 104.34 ( $\text{C}_3'$ ), 110.90 ( $\text{C}_7'$ ), 121.05 ( $\text{C}_4'$ ), 122.90 ( $\text{C}_5'$ ), 124.28 ( $\text{C}_6'$ ), 126.73 ( $\text{C}_3'\text{a}$ ), 127.01 ( $2\text{C}_2''$  or  $2\text{C}_3''$ ), 127.69 ( $2\text{C}_2''$  or  $2\text{C}_3''$ ), 128.14 ( $\text{C}_4''$ ), 138.87 ( $\text{C}_1''$ ), 154.10 ( $\text{C}_7'\text{a}$ ), 154.30 ( $\text{C}_2'$ ), 167.40 ( $\text{CH}_3\text{CO}$ ), 169.26 ( $\text{CONH}$ ) ppm.

IR (KBr) 3230, 1625 (br), 1520 (br), 1440, 1090, 1085, 890, 735, 690  $\text{cm}^{-1}$ ;

Mass spectrum,  $m/e$  (relative intensity) 322 (5), 279 (1), 264 (1), 234 (1), 215 (5), 189 (45), 146 (100), 130 (11), 118 (7), 91 (87), 65 (16).

High resolution mass spectrum,

Calcd for  $\text{C}_{19}\text{H}_{18}\text{N}_2\text{O}_3$  322.1317.

Found 322.1318.

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EXAMPLE 22

Preparation of (D,L)- $\alpha$ -Acetamido-N-benzyl-2-benzo[b]thiopheneacetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (1.00 g, 4 mmol) was suspended in anhydrous ethyl ether (15 mL) and then boron trifluoride etherate (0.91 g, 6.3 mmol) was rapidly added, and the resulting solution was stirred for 15 min. The benzo[b]thiophene (2.14 g, 16 mmol) was then added and the reaction was stirred at room temperature (3 d). The solution was poured into an ice-cold saturated aqueous solution of  $\text{NaHCO}_3$ , and then stirred for 15 min at 0 °C. The mixture was extracted with ethyl acetate (2 x), and the organic layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ) and evaporated in vacuo to give an orange oil. The oil was triturated with ethyl ether to yield a crystalline product which was filtered and further purified by flash chromatography (99:1 chloroform/methanol) to give the desired product.

Yield: 0.06 g (4%).

$R_f$  0.32 (99:1 chloroform/methanol).

mp 226-227 °C.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.94 (s,  $\text{CH}_3\text{CO}$ ), 4.34 (d,  $J = 5.7$  Hz,  $\text{CH}_2$ ), 5.86 (d,  $J = 8.1$  Hz,  $\text{CH}$ ), 7.20-7.38 (m,  $\text{C}_3\text{'H}$ ,  $\text{C}_6\text{'H}$ ,  $\text{C}_7\text{'H}$ ,  $\text{Pb}$ ), 7.77-7.80 (m,  $\text{C}_4\text{'H}$  or  $\text{C}_5\text{'H}$ ), 7.89-7.93 (m,  $\text{C}_4\text{'H}$  or  $\text{C}_5\text{'H}$ ), 8.76 (d,  $J = 8.1$  Hz,  $\text{NH}$ ), 8.97 (t,  $J = 5.7$  Hz,  $\text{NH}$ ).

$^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ) 22.34 ( $\text{CH}_3\text{CO}$ ), 42.38 ( $\text{CH}_2$ ), 52.70 ( $\text{CH}$ ), 122.15 ( $\text{C}_4\text{'}$  or  $\text{C}_7\text{'}$ ), 122.32 ( $\text{C}_4\text{'}$  or  $\text{C}_7\text{'}$ ), 123.45 ( $\text{C}_3\text{'}$ ), 124.37 ( $\text{C}_5\text{'}$  or  $\text{C}_6\text{'}$ ), 124.41 ( $\text{C}_5\text{'}$  or  $\text{C}_6\text{'}$ ), 126.89 ( $\text{C}_4\text{'}$ ), 127.27 ( $2\text{C}_2\text{'}$  or  $2\text{C}_3\text{'}$ ), 128.27 ( $2\text{C}_2\text{'}$  or  $2\text{C}_3\text{'}$ ), 138.84 ( $\text{C}_3\text{'a}$  or  $\text{C}_7\text{'a}$ ), 138.95 ( $\text{C}_3\text{'a}$  or  $\text{C}_7\text{'a}$ ), 142.58 ( $\text{C}_1\text{'}$ ), 168.65 ( $\text{CH}_3\text{CO}$ ), 169.12 ( $\text{CONH}$ ) ppm. [A distinct signal for the  $\text{C}_2\text{'}$  carbon was not detected and is presumed to coincide with the  $\text{C}_1\text{'}$  carbon at 142.58 ppm.].

IR (KBr) 3240, 1610 (br), 1510 (br), 1420, 1360, 1215, 1085, 885, 730, 710, 685  $\text{cm}^{-1}$ .

Mass spectrum,  $m/e$  (relative intensity) 338 (8), 295 (2), 205 (76), 162 (100), 135 (22), 108 (12), 91 (59).

Elemental Analysis:

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1      Calculated:      67.43% C; 5.36% H; 8.28% N.  
     Found:      67.21% C; 5.37 %H; 8.12% N.

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EXAMPLE 23

Preparation of (D,L)- $\alpha$ -Acetamido-N-benzyl-3-indoleacetamide.

N-Acetyl-D,L-ethoxyglycine-N-benzylamide (0.69 g, 2.75 mmol) was suspended in anhydrous ethyl ether (20 mL) and then boron trifluoride etherate (0.63 g, 4.40 mmol) was rapidly added, and the resulting solution was stirred for 15 min. The indole (1.30 g, 11.00 mmol) was then added and the reaction was stirred at room temperature (22 h). Petroleum ether (35-60 °C) was added to the reaction, and the resulting semisolid material filtered, and washed with petroleum ether (35-60 °C). Purification of the reaction mixture was accomplished by flash chromatography (98:2 chloroform/methanol) to produce the title compound as a white solid.

Yield: 0.25 g (18%).

R<sub>f</sub> 0.14 (95:5 chloroform/methanol)

mp 213-214 °C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.90 (s, CH<sub>3</sub>CO), 4.36 (d,  $J$  = 6.0 Hz, CH<sub>2</sub>), 5.72 (d,  $J$  = 7.2 Hz, CH), 6.90-7.37 (m, Ph, C<sub>2</sub>H), 7.02 (dd,  $J$  = 7.5 Hz,  $J$  = 7.5 Hz, C<sub>5</sub>H or C<sub>6</sub>H), 7.12 (dd,  $J$  = 7.5 Hz,  $J$  = 7.5 Hz, C<sub>5</sub>H or C<sub>6</sub>H), 7.39 (d,  $J$  = 7.5 Hz, C<sub>4</sub>H or C<sub>7</sub>H), 7.65 (d,  $J$  = 7.5 Hz, C<sub>4</sub>H or C<sub>7</sub>H), 7.86 (d,  $J$  = 7.2 Hz, NHCH), 8.13 (t,  $J$  = 6.0 Hz, NHCH<sub>2</sub>), 10.30-10.80 (br s, NH).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.32 (CH<sub>3</sub>CO), 42.23 (CH<sub>2</sub>), 49.98 (CH), 111.51 (C<sub>7</sub>'), 112.08 (C<sub>3</sub>'), 118.76 (C<sub>4</sub>' or C<sub>6</sub>'), 119.24 (C<sub>4</sub>' or C<sub>6</sub>'), 121.37 (C<sub>5</sub>'), 123.94 (C<sub>2</sub>'), 126.58 (C<sub>3</sub>'a), 126.71 (C<sub>4</sub>'), 127.33 (2C<sub>2</sub>'' or 2C<sub>3</sub>''), 128.18 (2C<sub>2</sub>'' or 2C<sub>3</sub>''), 136.28 (C<sub>7</sub>'a), 139.44 (C<sub>1</sub>''), 169.13 (CH<sub>3</sub>CO), 170.81 (CONH) ppm.

IR (KBr) 3260, 1610 (br), 1515 (br), 1450, 1420, 1370, 1350, 1235, 1095, 895, 735, 715, 695, 600 cm<sup>-1</sup>.

Mass spectrum, m/e (relative intensity) 321 (5), 278 (1), 264 (1), 233 (1), 214 (6), 187 (85), 171 (3), 145 (100), 118 (18), 91 (39).

Elemental Analysis:

Calculated: 71.01% C; 5.96% H; 13.06% N.

1 Found: 70.87% C; 6.15% H; 12.78% N.

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EXAMPLE 24

Preparation of (D, L)- $\alpha$ -Acetamido-N-benzyl-2-(5-methylpyrrole)acetamide.

5 N-Acetyl-D,L-ethoxyglycine-N-benzylamide (2.00 g, 8 mmol) was suspended in anhydrous ethyl ether (175 mL), and then boron trifluoride etherate (1.38 g, 9.7 mmol) was added and the resulting solution stirred (15 min). The 2-methylpyrrole (0.85 g, 10 mmol) was then added and the reaction mixture was stirred under N<sub>2</sub> (6 d), during which time the color of the reaction mixture turned reddish brown and a dark-brown deposit formed at the bottom of the flask. The clear solution was decanted and treated with an aqueous saturated NaHCO<sub>3</sub> solution containing ice (100 mL) for 30 min. The aqueous reaction mixture was extracted with ethyl acetate (3 x 30 mL). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and the solvent removed in vacuo. The brown oily residue was purified by flash column chromatography using 98:2 chloroform/methanol as the eluent to yield the desired compound. The product was recrystallized from ethyl acetate/hexane to give a light yellow amorphous solid.

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Yield 0.20 g (94%)

R<sub>f</sub> 0.44 (95:5, chloroform/methanol).

mp 167-168 °C.

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<sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.87 (s, CH<sub>3</sub>), 2.13 (s, COCH<sub>3</sub>), 4.27 (br s, CH<sub>2</sub>), 5.33 (d, J = 7.4 Hz, CH), 5.60 (s, C<sub>4</sub>H), 5.77 (s, C<sub>3</sub>H), 7.19-7.30 (m, 5 PhH), 8.22 (d, J = 7.4 Hz, NH), 8.45 (t, J = 5.5 Hz, NH), 10.38 (s, NH).

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<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 12.74 (CH<sub>3</sub>), 22.49 (COCH<sub>3</sub>), 42.11 (CH<sub>2</sub>), 51.21 (CH), 105.09 (C<sub>4</sub>), 106.07 (C<sub>3</sub>), 126.16 (C<sub>5</sub>), 126.64 (C<sub>4'</sub>), 126.85 (C<sub>2</sub>), 127.09 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.17 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 139.33 (C<sub>1'</sub>), 168.88 (COCH<sub>3</sub>), 169.79 (CONH) ppm.

IR (KBr) 3250, 1630, 1520, 1420, 1360, 1300, 1260, 1230, 1160, 1110, 1020 cm<sup>-1</sup>.

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Mass spectrum, m/e (relative intensity) 285 (M<sup>+</sup>, 10), 178 (20), 152 (24), 151 (100), 110 (12), 109 (93), 108 (22), 107 (25), 94 (16), 91 (43).

Elemental Analysis:

Calculated: 67.35% C; 6.71% H; 14.73% N.

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Found:

67.57% C; 6.90% H; 14.52% N.

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1 Synthesis of Unsubstituted and Substituted- $\alpha$ -Acetamido-N-benzyl-2-furanacetamides.

5 General Procedure. 4-Methylmorpholine (1 equiv) was added to a solution of  $\alpha$ -acetamido-2-furanacetic acid (1 equiv) in dry tetrahydrofuran (75 mL/10 mmol) at -10 to -15 °C under N<sub>2</sub>. After stirring (2 min), isobutyl chloroformate (1 equiv) was added leading to the precipitation of a white solid. The reaction was allowed to proceed for 2 additional minutes and then a solution of the substituted benzylamine (1 equiv) in tetrahydrofuran (10mL/10 mmol) was added over 5 min at -10 to -15 °C. The reaction mixture was allowed to stir at room temperature for 5 min and then the 4-methylmorpholine hydrochloride salt filtered. The organic layer was concentrated in vacuo, and the residue was triturated with ethyl acetate, and the remaining white solid filtered. Concentration of the ethyl acetate layer led to additional amounts of the white solid. The desired product was purified by either recrystallization, or flash chromatography of the combined solid material. Examples 25-32 were prepared according to this procedure.

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EXAMPLE 25

(D,L)- $\alpha$ -Acetamido-N-benzyl-2-furanacetamide.

Using benzyl amine (0.27 g, 2.56 mmol) and racemic  $\alpha$ -acetamido-2-furanacetic acid (0.47 g, 2.56 mmol) gave the desired compound.

The product was recrystallized from ethyl acetate to give a white solid.

Yield: 0.46 g (65%)

$R_f$  0.30 (98:2 chloroform/methanol).

mp 177-178 °C.

$^1H$  NMR (DMSO- $d_6$ )  $\delta$  1.90 (s,  $CH_3$ ), 4.31 (d,  $J = 6.0$  Hz,  $CH_2$ ), 5.58 (d,  $J = 8.1$  Hz,  $CH$ ), 6.27 - 6.33 (m,  $C_3H$ ), 6.40 - 6.44 (m,  $C_4H$ ), 7.20 - 7.36 (m, 5  $PhH$ ), 7.60 - 7.64 (m,  $C_5H$ ), 8.57 (d,  $J = 8.1$  Hz,  $NH$ ), 8.73 (t,  $J = 6.0$  Hz,  $NH$ ).

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EXAMPLE 26

(D,L)- $\alpha$ -Acetamido-N-(2-fluorobenzyl)-2-furanacetamide.

Using 2-fluorobenzylamine (1.13 g, 9.0 mmol) and racemic  $\alpha$ -acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) gave the desired product.  
Yield: 1.20 g (50%).

$R_f$  0.36 (96:4 chloroform/methanol).

mp 193-195 °C (recrystallized from EtOAc).

$^1H$  NMR (DMSO- $d_6$ )  $\delta$  1.89 (s, COCH<sub>3</sub>), 4.33 (d,  $J$  = 5.5 Hz, CH<sub>2</sub>), 5.58 (d,  $J$  = 8.0 Hz, CH), 6.28 (s, C<sub>4</sub>H), 6.29 (s, C<sub>3</sub>H), 7.62 (s, C<sub>5</sub>H), 7.13-7.35 (m, 4 ArH), 8.61 (d,  $J$  = 8.0 Hz, NH), 8.76 (t,  $J$  = 5.5 Hz, NH).

$^{13}C$  NMR (DMSO- $d_6$ ) 22.35 (COCH<sub>3</sub>), 36.12 (d,  $J_{CF}$  = 6.6 Hz, CH<sub>2</sub>), 50.88 (CH), 107.64 (C<sub>4</sub>), 110.43 (C<sub>3</sub>), 115.04 (d,  $J_{CF}$  = 21.4 Hz, C<sub>3'</sub>), 124.29 (d,  $J_{CF}$  = 4.2 Hz, C<sub>5'</sub>), 125.64 (d,  $J_{CF}$  = 15.0 Hz, C<sub>1'</sub>), 128.94 (d,  $J_{CF}$  = 9.0 Hz, C<sub>4'</sub> or C<sub>6'</sub>), 129.27 (d,  $J_{CF}$  = 5.5 Hz, C<sub>4'</sub> or C<sub>5'</sub>), 142.66 (C<sub>5</sub>), 151.07 (C<sub>2</sub>), 159.99 (d,  $J_{CF}$  = 244.4 Hz, C<sub>2'</sub>), 168.17 (COCH<sub>3</sub>), 169.24 (CONH) ppm.

IR (KBr) 3270, 1630, 1520, 1440, 1360, 1220, 1180, 1140, 1100, 1000, 740 cm<sup>-1</sup>.

Mass spectrum,  $m/e$  (relative intensity) 291 ( $M^+ + 1$ , 3), 274 (2), 247(3), 165 (4), 145 (10), 139 (98), 138 (46), 126 (7), 110 (10), 109 (65), 97 (93), 96 (100).

Elemental Analysis:

Calculated: 62.02% C; 5.21% H; 9.65% N.

Found: 62.20% C; 5.19% H; 9.69% N.

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EXAMPLE 27

(D,L)- $\alpha$ -Acetamido-N-(3-fluorobenzyl)-2-furanacetamide.

5 Making use of 3-fluorobenzylamine (1.13 g, 9.0 mmol) and racemic  $\alpha$ -acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) gave the desired product.  
Yield 1.90 g (80%).

R<sub>f</sub> 0.30 (96:4 chloroform/methanol).

10 mp 163-165 °C (recrystallized from ethyl acetate).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.89 (s, COCH<sub>3</sub>), 4.31 (d, J = 5.5 Hz, CH<sub>2</sub>), 5.55 (d, J = 7.8 Hz, CH), 6.31 (s, C<sub>4</sub>H), 6.42 (s, C<sub>3</sub>H), 6.98-7.37 (m, 4 ArH), 7.62 (s, C<sub>5</sub>H), 8.61 (d, J = 7.8 Hz, NH), 8.70 (t, J = 5.5 Hz, NH).

15 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.35 (COCH<sub>3</sub>), 41.71 (CH<sub>2</sub>), 51.01 (CH), 107.73 (C<sub>4</sub>), 110.59 (C<sub>3</sub>), 113.50 (d, J<sub>CF</sub> = 21.6 Hz, C<sub>2'</sub> or C<sub>4'</sub>), 113.60 (d, J<sub>CF</sub> = 22.3 Hz, C<sub>2'</sub> or C<sub>4'</sub>), 122.95 (br, C<sub>6'</sub>), 130.18 (d, J<sub>CF</sub> = 8.6 Hz, C<sub>5'</sub>), 142.21 (d, J<sub>CF</sub> = 7.5 Hz, C<sub>1'</sub>), 142.66 (C<sub>5</sub>), 151.03 (C<sub>2</sub>), 162.28 (d, J<sub>CF</sub> = 243.3 Hz, C<sub>3'</sub>), 168.23 (COCH<sub>3</sub>), 169.31 (CONH)  
20 ppm.

IR (KBr) 3230, 1630, 1540, 1440, 1360, 1220, 1140, 1000, 730 cm<sup>-1</sup>.

Mass spectrum, m/e (relative intensity) 290 (M<sup>+</sup>, 71), 231 (7), 165 (18), 140 (23), 130 (100), 126 (16), 109 (6), 97 (118), 96 (100), 96 (30).

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Elemental Analysis:

Calculated: 62.02% C; 5.21% H; 9.65% N.

Found: 61.97% C; 5.35% H; 9.53% N.

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EXAMPLE 28

(D, L)- $\alpha$ -Acetamido-N-(4-fluorobenzyl)-2-furanacetamide.

5 Using racemic  $\alpha$ -acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) and 4-fluorobenzylamine (1.13 g, 9.0 mmol) gave the desired product.

Yield 2.10 g (88%).

R<sub>f</sub> 0.30 (96:4 chloroform/methanol).

10 mp 188-190 °C (recrystallized from ethyl acetate).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.88 (s, COCH<sub>3</sub>), 4.27 (d, J = 5.5 Hz, CH<sub>2</sub>), 5.55 (d, J = 8.0 Hz, CH), 6.27 (s, 1H), 6.41 (s, 1H), 7.09-7.15 (m, 2ArH), 7.12-7.27 (m, 2 ArH), 7.61 (s, 1H), 8.58 (d, J = 8.0 Hz, NH), 8.75 (t, J = 5.5 Hz, NH).

15 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.28 (COCH<sub>3</sub>), 41.51 (CH<sub>2</sub>), 50.87 (CH), 107.52 (C<sub>4</sub>), 110.46 (C<sub>3</sub>), 114.90 (d, J<sub>CF</sub> = 21.1 Hz, C<sub>3'</sub>), 129.48 (d, J<sub>CF</sub> = 8.3 Hz, C<sub>2'</sub>), 135.23 (d, J<sub>CF</sub> = 3.2 Hz, C<sub>1'</sub>), 142.53 (C<sub>5</sub>), 151.08 (C<sub>2</sub>), 161.12 (d, J<sub>CF</sub> = 242.2 Hz, C<sub>4'</sub>), 167.95 (COCH<sub>3</sub>), 169.13 (CONH) ppm.

20 IR (KBr) 3230, 1620, 1500, 1360, 1320, 1260, 1210, 1140, 1000, 820, 780, 730 cm<sup>-1</sup>.

Mass spectrum, m/e (relative intensity) 291 (M<sup>+</sup>+1, 4), 165 (4), 140 (9), 139 (92), 138 (52), 124 (6), 109 (71), 97 (60), 96 (100).

Elemental Analysis:

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Calculated: 62.02% C; 5.21% H; 9.65% N.

Found: 61.76% C; 5.41% H; 9.43% N.

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EXAMPLE 29

(D, L)- $\alpha$ -Acetamido-N-(2,5-difluorobenzyl)-2-furanacetamide.

Using 2,5-difluorobenzylamine (1.30 g, 9.0 mmol) and racemic  $\alpha$ -acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) gave the desired product.

Yield 1.60 g (64%):

$R_f$  0.38 (96:4 chloroform/methanol).

mp 177-178 °C (recrystallized from ethyl acetate).

$^1H$  NMR (DMSO- $d_6$ )  $\delta$  1.89 (s, COCH<sub>3</sub>), 4.31 (d,  $J$  = 5.5 Hz, CH<sub>2</sub>), 5.55 (d,  $J$  = 7.7 Hz, CH), 6.32 (s, C<sub>4</sub>H), 6.43 (s, C<sub>3</sub>H), 7.22-7.25 (m, 3 ArH), 7.62 (s, C<sub>5</sub>H), 8.62 (d,  $J$  = 7.7 Hz, NH), 8.78 (t,  $J$  = 5.5 Hz, NH).

$^{13}C$  NMR (DMSO- $d_6$ ) 22.30 (COCH<sub>3</sub>), 35.98 (d,  $J_{CF}$  = 5.8 Hz, CH<sub>2</sub>), 51.02 (CH), 107.81 (C<sub>4</sub>), 110.58 (C<sub>3</sub>), 115.06 (dd,  $J_{CF}$  = 19.5, 25.6 Hz, C<sub>3'</sub> or C<sub>6'</sub>), 115.16 (dd,  $J_{CF}$  = 15.6, 24.7 Hz, C<sub>3'</sub> or C<sub>6'</sub>), 116.52 (dd,  $J_{CF}$  = 10.1, 23.9 Hz, C<sub>4'</sub>), 127.98 (dd,  $J_{CF}$  = 9.2, 17.7 Hz, C<sub>1'</sub>), 142.69 (C<sub>5</sub>), 150.78 (C<sub>2</sub>), 155.89 (d,  $J_{CF}$  = 239.0 Hz, C<sub>2'</sub> or C<sub>5'</sub>), 158.18 (d,  $J_{CF}$  = 238.8 Hz, C<sub>2'</sub> or C<sub>5'</sub>), 168.38 (COCH<sub>3</sub>), 169.35 (CONH) ppm.

IR (KBr) 3230, 1620, 1520, 1480, 1360, 1260, 1230, 1180, 1140, 1000, 860, 810, 730, 710  $cm^{-1}$ .

Mass spectrum,  $m/e$  (relative intensity) 309 ( $M^++1$ , 1), 266 (1), 222(1), 165 (5), 140 (5), 139 (61), 138 (36), 127 (37), 97 (44), 96 (100).

Elemental Analysis:

Calculated: 58.44% C; 4.58% H; 9.09% N.

Found: 58.68% C; 4.69% H; 8.87% N.

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EXAMPLE 30

1. (D, L)- $\alpha$ -Acetamido-N-(2,6-difluorobenzyl)-2-furanacetamide.

Making use of 2,6-difluorobenzylamine (1.30 g, 9.0 mmol) and racemic

$\alpha$ -acetamido-2-furanacetic acid (1.50 g, 8.2 mmol) the desired product was formed  
5 Yield 1.90 g (73%).

mp 237-239 °C (recrystallized from ethanol).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.86 (COCH<sub>3</sub>), 4.33 (d, J = 4.5 Hz, CH<sub>2</sub>), 5.53 (d, J = 8.3 Hz,  
CH), 6.17 (s, C<sub>4</sub>H), 6.38 (s, C<sub>3</sub>H), 7.05-7.10 (m, 2 ArH), 7.36-7.41 (m, 1 ArH), 7.60 (s,  
10 C<sub>5</sub>H), 8.52 (d, J = 8.3 Hz, NH), 8.66 (t, J = 4.5 Hz, NH).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  $\delta$  22.33 (COCH<sub>3</sub>), 30.74 (t, J<sub>CF</sub> = 4.4 Hz, CH<sub>2</sub>), 50.48 (CH),  
107.24 (C<sub>4</sub>), 110.40 (C<sub>3</sub>), 111.61 (dd, J<sub>CF</sub> = 8.0, 25.1 Hz, C<sub>3'</sub>, C<sub>5'</sub>), 113.67 (t, J<sub>CF</sub> =  
15 19.5 Hz, C<sub>1'</sub>), 129.98 (t, J<sub>CF</sub> = 10.5 Hz, C<sub>4'</sub>), 142.50 (C<sub>5</sub>), 151.23 (C<sub>2</sub>), 160.93 (d, J<sub>CF</sub>  
= 248.1, C<sub>2'</sub> or C<sub>6'</sub>), 161.10 (d, J<sub>CF</sub> = 248.1 Hz, C<sub>2'</sub> or C<sub>6'</sub>), 167.59 (COCH<sub>3</sub>), 169.00  
(CONH) ppm.

17 IR (KBr) 3230, 1620, 1530, 1460, 1360, 1320, 1260, 1220, 1160, 1140, 1030, 1000, 820,  
20 780, 750, 740, 710 cm<sup>-1</sup>.

Mass spectrum, m/e (relative intensity) 309 (M<sup>+</sup>+1, 4), 265 (2), 165 (4), 147 (7), 140  
(8), 139 (87), 138 (36), 127 (54), 97 (58), 96 (100).

Elemental Analysis:

25 Calculated: 58.44% C; 4.58% H; 9.09% N.  
Found: 58.62% C; 4.74% H; 8.99% N.

EXAMPLE 31

(D)-(-)  $\alpha$ -Acetamido-N-benzyl-2-furanacetamide.

Starting with D- $\alpha$ -acetamido-2-furanacetic acid (2.45 g, 13.38 mmol) and benzylamine (1.43 g, 13.38 mmol), the desired product was obtained.

Yield: 2.54 g (70%) The product was further recrystallized from ethyl acetate to give the title compound.

Yield: 2.30 g

mp 196-197 °C.

$[\alpha]^{26}_D [c = 1, \text{MeOH}] = -78.3^\circ$ . Addition of R(-)-mandelic acid to a  $\text{CDCl}_3$  solution of the product gave only one signal for the acetamide methyl protons.

Mass spectrum, m/e (relative intensity) 272 ( $\text{M}^+$ , 2), 184 (2), 165 (2), 140 (8), 139 (88), 138 (34), 97 (46), 96 (100), 91 (63).

Elemental Analysis:

Calculated: 66.16% C; 5.92% H; 10.29% N.

Found: 66.09% C; 6.01% H; 10.38% N.

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EXAMPLE 32

(L)-(+)- $\alpha$ -Acetamido-N-benzyl-2-furanacetamide.

Using L- $\alpha$ -acetamido-2-furanacetic acid (2.83 g, 15.46 mmol) and  
5 benzylamine (1.65 g, 15.46 mmol) gave 3.80 g of the enriched desired product.  $^1\text{H}$   
NMR analysis with R(-)-mandelic acid showed that it was greater than 80%  
enriched in the title compound. The pure L-enantiomer was obtained by  
recrystallization from absolute ethanol.

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Yield: 1.60 g.

mp 196-197 °C.

$[\alpha]^{26}_{\text{D}}[\text{c} = 1, \text{MeOH}] = +79.0^\circ$ .

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Mass spectrum, m/e (relative intensity) 273 ( $\text{M}^+ + 1$ , 3), 229 (2), 214 (2), 184 (1), 165  
(7), 157 (4), 140 (33), 139 (100), 138 (95), 97(98), 96 (100), 91 (98).

Elemental Analysis:

Calculated: 66.16% C; 5.92% H; 10.29% N.

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Found: 65.89% C; 5.86% H; 10.42% N.

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EXAMPLE 33

Resolution of (D, L)- $\alpha$ -Acetamido-2-furanacetic acid Using (R)-(+)- $\alpha$ -Methylbenzylamine and (S)-(-)- $\alpha$ -Methylbenzylamine.

(R)-(+)- $\alpha$ -Methylbenzylamine (13.22 g, 0.11 mol) was added to an absolute ethanol solution (550 mL) of racemic  $\alpha$ -acetamido-2-furanacetic acid (20.00 g, 0.11 mol). The resulting solution was cooled in the freezer overnight. The white precipitate (12.00 g) which separated upon cooling was filtered, and the mother liquid evaporated to give a salt which was later used for obtaining L- $\alpha$ -acetamido-2-furanacetic acid. The initial salt was recrystallized (3 x) from absolute ethanol to yield 4.00 g of the pure diastereomeric salt.

mp 173-175°C.

$[\alpha]^{26}_D [c=1, \text{MeOH}] = -108.3^\circ$

Elemental Analysis

Calculated: 63.14% C; 6.62% H; 9.21% N.

Found: 63.19% C; 6.62% H; 9.12% N.

The purified salt was treated with 5% aqueous  $\text{NH}_4\text{OH}$  solution, extracted with ethyl ether (3 x 50 mL), and then acidified with a 8.5% aqueous solution of  $\text{H}_3\text{PO}_4$  and then extracted with ethyl acetate (3 x 100 mL) to yield 2.45 g (25%) of D- $\alpha$ -acetamido-2-furanacetic acid.

mp 169-171°C.

$[\alpha]^{26}_D [c=1, \text{MeOH}] = -184.2^\circ$ .

Elemental Analysis:

Calculated: 52.46% C; 4.95% H; 7.65% N.

Found: 52.17% C; 4.89% H; 7.56% N.

The salt obtained after evaporation of the main mother

1 liquor was hydrolysed with 5% aqueous  $\text{NH}_4\text{OH}$  solution to give  
10.10 g of the enriched L- $\alpha$ -acetamido-2-furanacetic acid  
10  $[[\alpha]^{26}_D(c=1, \text{MeOH}) = +47.7^\circ]$ . (S)-(-) -methylbenzylamine (6.70  
5 g, 0.055 mol) was added to a solution of enriched L- $\alpha$ -acetamido-  
2-furanacetic acid (10.10 g, 0.055 mol) in absolute ethanol  
(275 mL). The white precipitate of the diastereoemeric salt  
(8.10 g) that separated upon cooling the solution in the  
10 freezer (1 h) was filtered. The salt was recrystallized  
from absolute ethanol (3 x) to yield 3.00g of the salt,  
mp 172-174°C.

15  $[\alpha]^{26}_D(c=1, \text{MeOH}) = +106^\circ$ .

Elemental Analysis:

Calculated: 63.14% C; 6.62% H; 9.21% N.

Found: 63.18% C; 6.47% H; 9.00% N.

20 The salt from the third recrystallization was treated  
with a 5% aqueous  $\text{NH}_4\text{OH}$  solution and extracted with ethyl ether  
(3 x 50 mL), and then acidified with a 8.5% aqueous solution  
of  $\text{H}_3\text{PO}_4$ , and then extracted with ethyl acetate (3  
25 x 100 mL) to give 1.63g (32%) of L- $\alpha$ -acetamido-2-furanacetic  
acid.

mp 169-171°C.

30  $[\alpha]^{26}_D(c=1, \text{MeOH}) = +182^\circ$ .

EXAMPLE 34

Enzymatic Separation of D(-)- $\alpha$ -acetamido-2-furanacetic acid (R-19) from DL ( $\pm$ )- $\alpha$ -acetamido-2-furanacetic acid.

DL ( $\pm$ )- $\alpha$ -acetamido-2-furanacetic acid (2.00 g, 10.9 mmol) was suspended in deionized  $H_2O$  (600mL). An aqueous solution of LiOH (1N) was added to this suspension dropwise until all of the acid had dissolved and the pH was 7.2. Acylase 1, Grade II (20 mg, activity = 900 units/mg, Sigma Chemical Company, Cat. No. A 8376) was then added to the above solution and the mixture stirred at 34-37°C (41h). The suspension was then cooled to room temperature and acidified to pH 1.5 with aqueous 1N HCl. The suspended material was filtered, and the filtrate was saturated with solid NaCl, and then extracted with ethyl acetate (3x250 mL). The combined ethyl acetate extracts was dried ( $Na_2SO_4$ ). The solvent was removed in vacuo and the residue was triturated with ethyl acetate (10mL). The white solid (0.75 g) that remained was filtered and was pure D(-)- $\alpha$ -acetamido-2-furanacetic acid; mp 168-169°C, mixed mp with an authentic sample 168-169°C;  $[\alpha]_D^{26}$  [c=1, MeOH] = -184.3°.

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EXAMPLE 35

Preparation of D,L- $\alpha$ -Acetamido-2-furanacetic Acid.

1 An ethereal solution of  $\text{ZnCl}_2$  (1 N, 28 mL, 0.028 mol) was added to a stirred  
5 solution of ethyl acetamido-2-bromoacetate (4.40 g, 0.019 mol) and furan (11.23 g,  
0.165 mol) in dry tetrahydrofuran (100 mL), and allowed to stir at room  
temperature (5 h). The mixture was then treated with  $\text{H}_2\text{O}$  (50 mL), the organic  
phase separated, and the aqueous layer extracted with  $\text{CH}_2\text{Cl}_2$  (2 x 100 mL). The  
10 organic layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ) and the volatile materials were  
removed by distillation in vacuo to give approximately 4.00 g (97%) of light-brown  
semi-solid material. TLC analysis showed a major spot at  $R_f$  0.30 (99:1  
chloroform/methanol). The desired compound, D,L-ethyl  
15  $\alpha$ -acetamido-2-furanacetate, was purified by flash column chromatography on  
silica gel using 99:1 chloroform/methanol as the eluent to give 3.60 g (87%) of a  
beige solid.  
mp 68-70 °C.

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D, L-Ethyl  $\alpha$ -acetamido-2-furanacetate (4.00 g, 19 mmol) was dissolved in  
90:10 ethanol/water (150 mL) and then KOH (2.00 g, 35 mmol) was added and the  
25 resulting solution stirred at room temperature (48 h). The reaction was  
concentrated in vacuo and the residue diluted with  $\text{H}_2\text{O}$  and then washed with  
ethyl ether (3 x 50 mL). The aqueous layer was then made acidic with a 8.5%  
aqueous solution of  $\text{H}_3\text{PO}_4$  and extracted with ethyl acetate (3 x 150 mL). The  
30 organic layers were combined, dried ( $\text{Na}_2\text{SO}_4$ ), evaporated to dryness in vacuo to  
give the desired compound.

Yield: 2.65 g (76%).

$R_f$  0.37 (8:1:1 isopropanol/ $\text{NH}_4\text{OH}$ / $\text{H}_2\text{O}$ ).

35 mp 172-174 °C.

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EXAMPLE 36

Synthesis of (D,L)-2-Acetamido-4-pentenoic Acid-N-benzylamide.

4-Methylmorpholine (0.55 g, 5.40 mmol) was added to a stirred solution of 2-acetamido-4-pentenoic acid (0.81 g, 5.18 mmol) in dry tetrahydrofuran (60 mL) at -10 to -15 °C under N<sub>2</sub>. After stirring (2 min), isobutyl chloroformate (0.75 g, 5.70 mmol) was added leading to the precipitation of a white solid. The reaction was allowed to proceed for 2 additional minutes and then a solution of benzylamine (0.61 g, 5.70 mmol) in tetrahydrofuran (10 mL) was added slowly at -10 to -15 °C. After stirring (5 min) at room temperature, the insoluble salt was removed by filtration. The filtrate was evaporated to dryness and the residue was triturated with ethyl acetate, and the remaining white solid was filtered to yield the desired product.

Yield 0.81 g (64%).

R<sub>f</sub> 0.36 (4% methanol/chloroform).

mp 118-120 °C (recrystallized from ethyl acetate/cyclohexane).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.83 (s, COCH<sub>3</sub>), 2.22-2.49 (m, CH<sub>2</sub>CH=CH<sub>2</sub>), 4.26 (d, J = 5.3 Hz, CH<sub>2</sub> Ph), 4.25-4.33 (m, CH), 4.99-5.09 (m, CH<sub>2</sub>CH=CH<sub>2</sub>), 7.21-7.29 (m, 5 PhH), 8.05 (d, J = 7.6 Hz, NH), 8.46 (br s, NH).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.41 (COCH<sub>3</sub>), 36.24 (CH<sub>2</sub>CH=CH<sub>2</sub>), 41.91 (CH<sub>2</sub>Ph), 52.20 (CH), 117.15 (CH<sub>2</sub>CH=CH<sub>2</sub>), 126.54 (C<sub>4</sub>'), 126.99 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.04 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 134.25 (CH<sub>2</sub>CH=CH<sub>2</sub>), 139.22 (C<sub>1</sub>'), 169.02 (COCH<sub>3</sub>), 170.96 (CONH) ppm.

Mass spectrum, m/e (relative intensity) 246 (M<sup>+</sup>, 4), 205 (4), 163 (15), 140 (8), 106 (33), 91 (77), 70 (100).

Elemental Analysis:

Calculated:

Found:

68.27% C; 7.37% H; 11.37% N.

68.55% C; 7.31% H; 11.48% N.

1 Mass spectrum m/e (relative intensity) 292 ( $M^{++1}$ , 1), 233 (8), 158 (19), 157 (100),  
116 (26), 115 (100), 106 (29), 91 (72).

Elemental Analysis:

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Calculated:

61.84% C; 7.26% H; 14.42% N.

Found:

61.67 % C; 7.10% H; 14.14% N.

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EXAMPLE 37

Synthesis of (D,L)-2-Acetamido-N-benzyl-2-(1-morpholine)acetamide.

A mixture of ethyl 2-acetamido-2-(1-morpholine)acetate (0.59 g, 2.56 mmol),  
 5 benzylamine (0.28 g, 2.82 mmol) and sodium cyanide (0.01 g, 0.26 mmol) in  
 methanol (5 mL) was stirred at 50-55 °C for 18 hr. The solvent was removed in  
vacuo and the residue triturated with ethyl acetate (5 mL). The white solid (0.35 g)  
 that remained was collected by filtration and identified as the desired compound.  
 10 The filtrate was concentrated and the residue purified by flash column  
 chromatography (2% methanol/chloroform) on SiO<sub>2</sub>. The initial fractions gave a  
 trace amount (0.09 g) of (D,L)-2-acetamido-N-benzyl-2-(N-benzylamine)acetamide.  
 Continued elution gave additional amounts (0.20 g) of the title compound.

15 *(D,L)-2-Acetamido-N-benzyl-2-(N-benzylamine)acetamide:*

Yield: 0.09 g (11 %).

mp 135-138 °C.

1H NMR (DMSO-d<sub>6</sub>) δ 1.83 (s, COCH<sub>3</sub>), 3.56 (d, J = 13.6 Hz, NHCH), 3.66 (d, J =  
 20 13.6 Hz, NHCH), 4.23 (d, J = 5.4 Hz, CH<sub>2</sub>), 4.89 (d, J = 8.0 Hz, CH), 7.05-7.38 (m, 10  
 PhH), 8.20 (d, J = 8.0 Hz, NH), 8.51 (t, J = 5.4 Hz, NH).

13C NMR (DMSO-d<sub>6</sub>) 22.63 (COCH<sub>3</sub>), 42.11 (CH<sub>2</sub>), 48.57 (NHCH<sub>2</sub>), 64.41 (CH),  
 25 126.65 (C<sub>4</sub>), 126.70 (C<sub>4</sub>'), 127.13, 128.00, 128.13, 128.22, 139.24 (C<sub>1</sub> or C<sub>1</sub>'), 140.12 (C<sub>1</sub>  
 or C<sub>1</sub>'), 169.61 (COCH<sub>3</sub>), 169.90 (CONH) ppm.

*(D,L)-2-Acetamido-N-benzyl-2-(1-morpholine)acetamide.*

Yield: 0.48 g (64%).

30 R<sub>f</sub> 0.35 (4% methanol/chloroform).

mp 171-172 ° (recrystallized from ethyl acetate).

1H NMR (DMSO-d<sub>6</sub>) δ 1.86 (s, COCH<sub>3</sub>), 2.30-2.40 (m, CH<sub>2</sub>NCH<sub>2</sub>), 3.51 (br s,  
 CH<sub>2</sub>OCH<sub>2</sub>), 4.18-4.33 (m, CH<sub>2</sub>), 5.07 (d, J = 8.9 Hz, CH), 7.18-7.25 (m, 5 PhH), 8.23  
 35 (d, J = 8.9 Hz, NH), 8.58 (br s, NH).

13C (DMSO-d<sub>6</sub>) 22.39 (COCH<sub>3</sub>), 42.20 (CH<sub>2</sub>), 48.43 (CH<sub>2</sub>NCH<sub>2</sub>), 66.03 (CH), 69.24  
 (CH<sub>2</sub>OCH<sub>2</sub>), 126.76 (C<sub>4</sub>'), 127.13 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.23 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 139.42 (C<sub>1</sub>'),

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EXAMPLE 38

Synthesis of (D,L)-Ethyl 2-acetamido-2-(ethylamino)acetate.

A cold (-78 °C) solution of ethyl 2-acetamido-2-bromoacetate (2.10 g, 9.38 mmol) in dry tetrahydrofuran (80 mL) was added slowly into a cooled (-78 °C) tetrahydrofuran (20 mL) solution of methylamine (1.40 g, 31.04 mmol) over a period of 20 min. The reaction was stirred at -78 °C (1 h), and then at room temperature (1 h). The precipitated salt was filtered and the filtrate concentrated. The residue was purified by flash column chromatography on SiO<sub>2</sub> using 3% methanol/chloroform as the eluent to yield the desired compound as a light yellow oil.

Yield: 0.90 (51%).

R<sub>f</sub> 0.36 (4% methanol/chloroform).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) 0.93 (t, J = 6.7 Hz, NHCH<sub>2</sub>CH<sub>3</sub>), 1.12 (t, J = 6.8 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.87 (s, COCH<sub>3</sub>), 2.48 (q, J = 6.7 Hz, NHCH<sub>2</sub>CH<sub>3</sub>), 4.05 (q, J = 6.8 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 5.05 (d, J = 7.1 Hz, CH), 7.09 (d, J = 7.1 Hz, NH).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) 13.64 (NHCH<sub>2</sub>CH<sub>3</sub>), 14.55 (OCH<sub>2</sub>CH<sub>3</sub>), 22.53 (COCH<sub>3</sub>), 39.06 (NHCH<sub>2</sub>CH<sub>3</sub>), 61.38 (CH), 64.14 (OCH<sub>2</sub>CH<sub>3</sub>), 170.09 (COCH<sub>3</sub>), 170.20 (COOCH<sub>2</sub>CH<sub>3</sub>) ppm.



EXAMPLE 39

Using the procedures described herein, the following examples are also prepared:

(D,L)- $\alpha$ -Acetamido-N-benzyl-3-furanacetamide

(D,L)- $\alpha$ -Acetamido-N-(2-fluorobenzyl)-3-furanacetamide

(D,L)- $\alpha$ -Acetamido-N-(3-fluorobenzyl)-3-furanacetamide

(D,L)- $\alpha$ -Acetamido-N-(4-fluorobenzyl)-3-furanacetamide

$\alpha$ -Acetamido-N-benzyl-2-aminoacetamide

1 Preparation of  $\alpha$ -Heteroatom Substituted Amino Acids. Synthesis of Ethyl 2-  
5 Acetamido-2-substituted Acetates. General Procedure.

5 A cooled (-78 °C) solution of ethyl 2-bromo-2-acetamidoacetate (1  
equiv) in THF (1 mmol/10 mL) was added slowly to a THF (1 mmol/4 mL) solution  
of the nitrogen nucleophile (5-10 equiv) at -78 °C. The reaction was stirred at this  
temperature (0.5 h) and then at room temperature (1 h). The insoluble materials  
10 were filtered and washed with THF. The filtrate was concentrated in vacuo and  
the residue was purified by flash chromatography on SiO<sub>2</sub> gel (using the indicated  
solvent as the eluent) to give the desired product.

15 Using this procedure the following examples were  
prepared.

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EXAMPLE 40

1 Synthesis of Ethyl 2-Acetamido-2-aminoacetate.

Ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) and liquid NH<sub>3</sub> (5-6 equiv) yielded a light brown residue, which on purification by flash column chromatography on SiO<sub>2</sub> gel (5% MeOH/CHCl<sub>3</sub>) gave the desired product as a yellow oil.

Yield: 1.00 g (70%).

R<sub>f</sub> 0.21 (5% MeOH/CHCl<sub>3</sub>).

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.31 (t, J = 7.1 Hz, 3 H), 2.03 (s, 3 H), 2.61 (br s, 2 H), 4.24 (q, J = 7.1 Hz, 2 H), 5.21 (d, J = 7.1 Hz, 1 H), 7.50 (d, J = 7.1 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) 13.72, 22.68, 59.70, 61.73, 170.40, 170.68 ppm.

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EXAMPLE 41

1 Synthesis of Ethyl 2-Acetamido-2-(methylamino)acetate.

Use of ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) and MeNH<sub>2</sub> (2.50 g, 80.6 mmol) gave an oily residue (1.50 g). The residue was purified by flash column chromatography on SiO<sub>2</sub> gel (3% MeOH/CHCl<sub>3</sub>) to yield the desired product as an oil.

Yield: 1.00 g (65%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.32 (t, J = 7.1 Hz, 3 H), 2.07 (s, 3 H), 2.36 (s, 3 H), 4.26 (q, J = 7.1 Hz, 2 H), 5.20 (d, J = 7.4 Hz, 1 H), 6.60 (br s, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) 14.02, 23.06, 30.84, 62.04, 65.72, 170.09, 170.40 ppm.

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EXAMPLE 42

1 Synthesis of Ethyl 2-Acetamido-2-(N,N-dimethylamino)acetate.

Ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) and Me<sub>2</sub>NH (5-6 equiv) gave the desired product as a yellow oil.

5 Yield: 1.50 g (89%).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.25 (t, J = 7.1 Hz, 3 H), 2.02 (s, 3 H), 2.23 (s, 6 H), 4.10-4.25 (m, 2 H), 5.24 (d, J = 8.3 Hz, 1 H), 6.59 (d, J = 8.3 Hz, 1 H).

<sup>13</sup>C NMR (CDCl<sub>3</sub>) 14.05, 23.00, 40.28 (2 C), 61.84, 69.24, 169.38, 170.57 ppm.

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EXAMPLE 431 Synthesis of Ethyl 2-Acetamido-2-(4-morpholine)acetate.

Using morpholine (1.71 g, 19.64 mmol) and ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) gave an oily residue, which was purified by  
5 flash column chromatography on SiO<sub>2</sub> gel (2% MeOH/CHCl<sub>3</sub>) to give the desired product as a thick oil.

Yield: 1.90 g (93%).

R<sub>f</sub> 0.29 (3% MeOH/CHCl<sub>3</sub>).

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.32 (t, J = 6.8 Hz, 3 H), 2.07 (s, 3 H), 2.43-2.72 (m, 4 H), 3.58-3.78 (m, 4 H), 4.26 (q, J = 6.8 Hz, 2 H), 5.27 (d, J = 7.9 Hz, 1 H), 6.39 (d, J = 7.9 Hz, 1 H).

15 <sup>13</sup>C NMR (CDCl<sub>3</sub>) 14.21, 23.25, 48.47 (2 C), 62.06, 66.71 (2 C), 69.22, 169.00, 170.46 ppm.

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EXAMPLE 44

1 Synthesis of Ethyl 2-Acetamido-2-(N-anilino)acetate.

Use of aniline (1.83 g, 19.6 mmol) and ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.93 mmol) provided a brown residue which was  
5 purified by flash column chromatography on SiO<sub>2</sub> gel (CHCl<sub>3</sub>-2% MeOH/CHCl<sub>3</sub> gradient) to yield the desired product.

Yield: 1.80 g (85%).

R<sub>f</sub> 0.52 (4% MeOH/CHCl<sub>3</sub>).

10 mp 87-89 °C (recrystallized from ethyl acetate/petroleum ether)..

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.29 (t, J = 7.1 Hz, 3 H), 1.84 (s, 3 H), 4.27 (q, J = 7.1 Hz, 2 H), 5.89 (d, J = 8.2 Hz, 1 H), 6.43 (d, J = 8.2 Hz, 1 H), 6.68-6.71 (m, 2 H), 6.80-6.83 (m, 1 H), 7.17-7.22 (m, 2 H). The remaining amino proton was not detected.

15 <sup>13</sup>C NMR (CDCl<sub>3</sub>) 13.96, 22.98, 60.19, 62.41, 113.87 (2 C), 119.29, 129.37 (2 C), 144.09, 169.77, 170.14 ppm.

IR (KBr) 3340, 1720, 1635, 1590, 1490, 730, 710 cm<sup>-1</sup>.

Mass spectrum (FD) 237 (M<sup>++1</sup>).

20 Elemental analysis

Calculated for C <sub>12</sub> H <sub>16</sub> N <sub>2</sub> O <sub>3</sub>	61.00% C;	6.83% H;	11.86% N.
Found	60.88% C;	6.56% H;	12.00% N.

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EXAMPLE 45

1 Synthesis of Ethyl 2-Acetamido-2-(N-(3-pyrazolylamino))acetate.

Using ethyl 2-bromo-2-acetamidoacetate (2.00 g, 8.92 mmol) and 3-aminopyrazole (1.85 g, 22.32 mmol) and purification of the reaction product by  
5 chromatography on SiO<sub>2</sub> gel (2% MeOH/CHCl<sub>3</sub>) gave the desired product as a yellow oil.

Yield: 1.80 g (89%).

R<sub>f</sub> 0.35 (8% MeOH/CHCl<sub>3</sub>).

10 <sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.21 (t, J = 7.1 Hz, 3 H), 1.89 (s, 3 H), 4.20 (q, J = 7.1 Hz, 2 H),  
5.64 (d, J = 1.8 Hz, 1 H), 5.71 (br s, 1 H), 5.73 (d, J = 7.1 Hz, 1 H), 7.29 (d, J =  
1.8 Hz, 1 H), 7.98 (d, J = 7.1 Hz, 1 H). The remaining amino proton was not  
15 detected.  
<sup>13</sup>C NMR (CDCl<sub>3</sub>) 13.73, 22.49, 61.41, 62.02, 91.79, 130.53, 153.02, 169.96, 170.93 ppm.

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EXAMPLE 46

1 Synthesis of Ethyl 2-Acetamido-2-(N-hydroxyamino)acetate.

Using ethyl 2-bromo-2-acetamidoacetate (2.10 g, 9.37 mmol) and anhydrous  $\text{NH}_2\text{OH}$  (0.93 g, 28.00 mmol) gave an oily residue. The residue was purified by flash column chromatography on  $\text{SiO}_2$  gel (5%  $\text{MeOH}/\text{CHCl}_3$ ) to give the desired product. The product was recrystallized from  $\text{EtOH}$  to give a white flaky solid.

Yield: 1.00 g (61%).

10  $R_f$  0.24 (5%  $\text{MeOH}/\text{CHCl}_3$ ).

mp 119-121 °C.

15  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.19 (t,  $J = 6.9$  Hz, 3 H), 1.87 (s, 3 H), 4.10 (q,  $J = 6.9$  Hz, 2 H), 5.09 (dd,  $J = 4.0, 8.0$  Hz, 1 H), 6.06 (br s, 1 H), 7.63 (s, 1 H), 8.50 (d,  $J = 8.0$  Hz, 1 H).

$^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ) 14.05, 22.46, 60.82, 67.37, 169.19, 169.48 ppm.

IR (KBr) 3300, 1750, 1660, 1540, 1390, 610  $\text{cm}^{-1}$ .

20 Mass spectrum (FD) 177 ( $\text{M}^++1$ ).

Elemental analysis

Calculated for  $\text{C}_6\text{H}_{12}\text{N}_2\text{O}_4$  40.91% C; 6.87% H; 15.90% N.

Found 40.79% C; 6.87% H; 15.90% N.

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EXAMPLE 47

1 Synthesis of Ethyl 2-Acetamido-2-(N-(N-methylhydroxyamino))acetate.

MeNH<sub>2</sub>OH (17.39 mmol) (prepared from MeNH<sub>2</sub>OH·HCl (2.00 g, 23.95 mmol) and NaOMe (0.94 g, 17.39 mmol)), and ethyl 2-bromo-2-acetamidoacetate (1.00 g, 4.46 mmol) gave an oily residue. The residue was triturated with EtOAc (5 mL) and the solid that remained was filtered and recrystallized from EtOH to give the desired product as a white solid.

Yield: 0.70 g (82%).

10  $R_f$  0.34 (5% MeOH/CHCl<sub>3</sub>).

mp 148-150 °C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.17 (t, J = 7.0 Hz, 3 H), 1.89 (s, 3 H), 2.37 (s, 3 H), 4.00-4.20 (m, 2 H), 5.04 (d, J = 9.2 Hz, 1 H), 8.17 (s, 1 H), 8.43 (d, J = 9.2 Hz, 1 H).

15 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 14.04, 22.28, 43.78, 62.79, 71.46, 168.29, 170.23 ppm.

IR (KBr) 3320, 3200 (br), 1760, 1660, 1530, 1470, 720, 640 cm<sup>-1</sup>.

Mass spectrum (FD) 192 (M<sup>++</sup>1).

Elemental analysis

20	Calculated for C <sub>7</sub> H <sub>14</sub> N <sub>2</sub> O <sub>4</sub> ·0.25 H <sub>2</sub> O	43.18% C;	7.51% H;	14.39% N.
	Found	43.28% C;	7.25% H;	14.64% N.

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EXAMPLE 48

1 Synthesis of Ethyl 2-Acetamido-2-(N-(N,O-dimethylhydroxyamino))acetate.

MeNHOMe (17.40 mmol) (prepared from MeNHOMe·HCl (2.18 g, 22.32 mmol) and NaOMe (0.94 g, 17.40 mmol)) and ethyl 2-bromo-2-acetamido-  
5 acetate (1.00 g, 4.46 mmol) gave a residue which was purified by flash column chromatography on SiO<sub>2</sub> gel (1% MeOH/CHCl<sub>3</sub>) to give the desired product as an oil.

Yield: 0.60 g (66%).

10 R<sub>f</sub> 0.53 (2% MeOH/CHCl<sub>3</sub>).

<sup>1</sup>H NMR (CDCl<sub>3</sub>) δ 1.35 (t, J = 7.0 Hz, 3 H), 2.12 (s, 3 H), 2.62 (s, 3 H), 3.46 (s, 3 H),  
4.30 (q, J = 7.0 Hz, 2 H), 5.36 (d, J = 8.9 Hz, 1 H), 6.66 (d, J = 8.9 Hz, 1 H).

15 <sup>13</sup>C NMR (CDCl<sub>3</sub>) 14.06, 22.89, 40.30, 60.01, 61.89, 70.16, 168.14, 170.53 ppm.

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1 Synthesis of 2-Acetamido-N-benzyl-2-substituted Acetamides. General Procedure.

5 A mixture of the ethyl 2-substituted-2-acetamidoacetate (1 equiv),  
benzylamine (1.2 equiv), and NaCN (0.1 equiv) in MeOH (1 mmol/25 mL) was  
stirred at 45-50 °C (18 h). The solvent was removed in vacuo and the residue was  
purified using either trituration with EtOAc or flash column chromatography on  
SiO<sub>2</sub> gel with the indicated solvent as the eluent.

10 Using this procedure the following examples were  
prepared.

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EXAMPLE 49

1 Synthesis of 2-Acetamido-N-benzyl-2-aminoacetamide.

Ethyl 2-acetamido-2-aminoacetate (1.00 g, 6.25 mmol), benzylamine (0.80 g, 7.5 mmol) and NaCN (0.03 g, 0.61 mmol) gave a residue which solidified on standing (18 h). The reaction mixture was triturated with EtOAc (20 mL). The white solid which remained was filtered and then further purified by recrystallization from EtOAc.

Yield: 1.00 g (72%).

10  $R_f$  0.21 (5% MeOH/CHCl<sub>3</sub>).

mp 131-133 °C (dec.).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.83 (s, 3 H), 2.35 (br s, 2 H), 4.28 (d, J = 4.4 Hz, 2 H), 4.91 (d, J = 7.0 Hz, 1 H), 7.20-7.32 (m, 5 H), 8.31 (br s, 1 H), 8.51 (br s, 1 H).

15 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.66, 42.05, 60.29, 126.67, 127.10 (2 C), 128.18 (2 C), 139.23, 169.24, 170.67 ppm.

IR (KBr) 3300, 1650 (br), 1530 (br), 1450, 740 cm<sup>-1</sup>.

20 Mass spectrum, m/e (relative intensity) 222 (M<sup>+</sup>+1, 100), 221 (M<sup>+</sup>, 29), 133 (8).

Elemental analysis

Calculated for C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub> 59.71% C; 6.83% H; 18.99% N.

Found 59.86% C; 6.88% H; 18.72% N.

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EXAMPLE 50

1 Synthesis of 2-Acetamido-N-benzyl-2-(methylamino)acetamide.

Ethyl 2-acetamido-2-(methylamino)acetate (1.50 g, 8.63 mmol),  
benzylamine (1.11 g, 10.35 mmol) and NaCN (0.04 g, 0.82 mmol) gave a brown  
5 residue which was purified by flash column chromatography on SiO<sub>2</sub> gel (2%  
MeOH/CHCl<sub>3</sub>) to yield the desired product.

Yield: 1.00 g (49%).

R<sub>f</sub> 0.33 (3% MeOH/CHCl<sub>3</sub>).

10 mp 115-117 °C (recrystallized from ethyl acetate/petroleum ether).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.87 (s, 3 H), 2.18 (s, 3 H), 4.20-4.29 (m, 2 H), 4.87 (d, J = 7.9  
Hz, 1 H), 7.24-7.35 (m, 5 H), 8.14 (d, J = 7.9 Hz, 1 H), 8.55 (br s, 1 H). The  
remaining amino proton was not detected.

15 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.52, 31.37, 42.04, 65.99, 126.68, 127.12 (2 C), 128.18 (2 C),  
139.28, 169.51, 169.83 ppm.

IR (KBr) 3240, 1610 (br), 1500 (br), 1430, 725, 670 cm<sup>-1</sup>.

20 Elemental analysis

Calculated for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub> 61.26% C; 7.28% H; 17.86% N.

Found 61.12% C; 7.01% H; 17.71% N.

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EXAMPLE 51

1 Synthesis of 2-Acetamido-N-benzyl-2-(ethylamino)acetamide.

Using ethyl 2-acetamido-2-(ethylamino)acetate (0.90 g, 4.79 mmol), benzylamine (0.62 g, 5.75 mmol), and NaCN (0.03 g, 0.51 mmol) gave an oily  
5 residue which was purified by flash column chromatography on SiO<sub>2</sub> gel (3% MeOH/CHCl<sub>3</sub>) to give the desired product as a white solid.

Yield: 0.35 g (29%).

R<sub>f</sub> 0.34 (4% MeOH/CHCl<sub>3</sub>).

10 mp 123-125 °C (recrystallized from ethyl acetate/hexane).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 0.93 (t, J = 6.8 Hz, 3 H), 1.81 (s, 3 H), 2.08 (br s, 1 H), 2.40-2.48  
(m, 2 H), 4.22 (d, J = 5.5 Hz, 2 H), 4.90 (d, J = 7.8 Hz, 1 H), 7.20-7.27 (m, 5 H),  
8.08 (d, J = 7.8 Hz, 1 H), 8.48 (t, J = 5.5 Hz, 1 H).

15 <sup>13</sup>C NMR (CDCl<sub>3</sub>) 15.14, 22.97, 37.65, 43.53, 65.68, 127.44 (2 C), 127.50, 128.64 (2 C),  
137.73, 169.75, 171.20 ppm.

IR (KBr) 3250, 1620 (br), 1510 (br), 1450 (br), 740, 680 cm<sup>-1</sup>.

20 Elemental analysis

Calculated for C<sub>13</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub> 62.63% C; 7.68% H; 16.85% N.

Found 62.69% C; 7.49% H; 16.65% N.

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EXAMPLE 52

1 Synthesis of 2-Acetamido-N-benzyl-2-(N-anilino)acetamide.

Employing ethyl 2-acetamido-2-(N-anilino)acetate (2.00 g, 8.47 mmol), benzylamine (1.09 g, 10.00 mmol), and NaCN (0.04 g, 0.84 mmol) gave a white solid which separated during the course of the reaction. The precipitate was filtered and purified by recrystallization from absolute EtOH to give the desired product.

Yield: 1.10 g (44 %).

10 mp 183-185 °C.

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.84 (s, 3 H), 4.31 (d,  $J$  = 5.8 Hz, 2 H), 5.67 (t,  $J$  = 8.1 Hz, 1 H), 6.04 (d,  $J$  = 8.1 Hz, 1 H), 6.59-6.64 (m, 1 H), 6.70-6.72 (m, 2 H), 7.06-7.11 (m, 2 H), 7.20-7.33 (m, 5 H), 8.41 (d,  $J$  = 8.1 Hz, 1 H), 8.72 (t,  $J$  = 5.8 Hz, 1 H).

15  $^{13}\text{C}$  NMR (DMSO- $d_6$ ) 22.46, 42.25, 60.42, 113.21 (2 C), 117.22, 126.72, 127.16 (2 C), 128.18 (2 C), 128.77 (2 C), 138.99, 145.88, 168.65, 169.70 ppm.

IR (KBr) 3270, 1630, 1520, 1490, 1430, 740, 690  $\text{cm}^{-1}$ .

20 Mass spectrum,  $m/e$  (relative intensity) 297 ( $M^+$ , 2), 239 (7), 164 (28), 163 (100), 122 (20), 121 (100), 106 (47), 104 (65), 93 (63), 91 (77).

Elemental analysis

Calculated for  $\text{C}_{17}\text{H}_{19}\text{N}_3\text{O}_2$  68.67% C; 6.44% H; 14.13% N.

25 Found 68.94% C; 6.42% H; 13.92% N.

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## EXAMPLE 53

1 Synthesis of 2-Acetamido-N-benzyl-2-(N-(3-pyrazolylamino))acetamide.

A solution of ethyl 2-acetamido-2-(N-(3-pyrazolylamino))acetate (1.60 g, 7.1 mmol) in MeOH (40 mL) containing benzylamine (0.83 g, 7.8 mmol) and  
 5 NaCN (50 mg, 1 mmol) was stirred at 45-55 °C (18 h). TLC analysis (8% MeOH/CHCl<sub>3</sub>) of the reaction mixture indicated the presence of only a minor amount of product. A second lot of NaCN (50 mg, 1 mmol) was then added and the reaction was allowed to proceed at 45-55 °C (6 h) and then at room temperature  
 10 (48 h). The solvent was removed in vacuo and the residue was triturated with EtOAc (15 mL). The insoluble solid that remained was filtered and purified by flash column chromatography on SiO<sub>2</sub> gel (7% MeOH/CHCl<sub>3</sub>) to give the desired product.

15 Yield: 0.90 g (44%).

R<sub>f</sub> 0.35 (8% MeOH/CHCl<sub>3</sub>).

mp 135-137 °C.

20 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.82 (s, 3 H), 4.29 (d, J = 5.9 Hz, 2 H), 5.51-5.55 (m, 3 H), 7.18-7.40 (m, 6 H), 8.36 (br s, 1 H), 8.53 (br s, 1 H), 11.66 (br s, 1 H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.59, 42.29, 61.79, 90.68, 126.67, 127.07 (2 C), 128.17 (2 C), 129.10, 139.41, 153.53, 169.19, 169.67 ppm.

25 IR (KBr) 3230 (br), 1620 (br), 1500 (br), 1430, 730, 690 cm<sup>-1</sup>.

Mass spectrum, m/e (relative intensity) 288 (M<sup>+</sup>+1, 64), 287 (M<sup>+</sup>, 2), 230 (28), 229 (100), 153 (46).

## Elemental analysis

30	Calculated for C <sub>14</sub> H <sub>17</sub> N <sub>5</sub> O <sub>2</sub> ·0.5 H <sub>2</sub> O	56.47% C;	6.12% H;	23.63% N.
	Found	56.63% C;	5.79% H;	23.43% N.

1 Preparation of Functionalized  $\alpha$ -Heteroatom Substituted Amino Acids. General  
2 Procedure.

3 A BBr<sub>3</sub> solution (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 1.1 equiv) was added to a solution of  
4 2-acetamido-N-benzyl-2-ethoxyacetamide (1 equiv) in CH<sub>2</sub>Cl<sub>2</sub> (10 mmol/125 mL).  
5 The mixture was stirred at room temperature (5 h) and then concentrated to  
6 dryness in vacuo to give 2-acetamido-N-benzyl-2-bromoacetamide as a pale yellow  
7 crystalline material. The bromo adduct was then dissolved in THF (10 mmol/250  
8 mL), cooled (-78 °C), and then added over a 15 min interval to a cooled (-78 °C)  
9 solution of the heteroatom nucleophile in THF (1 mmol/1 mL). The reaction  
10 mixture was stirred at this temperature (30 min) and then at room temperature  
11 (90 min). The insoluble salts were filtered and the filtrate concentrated in vacuo.  
12 The residue was then purified by flash column chromatography on SiO<sub>2</sub> gel using  
13 the indicated solvent as the eluent.

14 Using this procedure the following examples were  
15 prepared.

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EXAMPLE 541 Synthesis of 2-Acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide.

By making use of 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), BBr<sub>3</sub> (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 13.2 mL, 13.2 mmol), and Me<sub>2</sub>NH (5-6 equiv) was obtained a brown residue which was purified by flash column chromatography on SiO<sub>2</sub> gel (2.5% MeOH/CHCl<sub>3</sub>) to give the desired product. The product was recrystallized from ethyl acetate/hexane to give light yellow cubic crystals.

Yield: 1.20 g (40%).

1.0 R<sub>f</sub> 0.39 (5% MeOH/CHCl<sub>3</sub>).

mp 104-106 °C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.91 (s, 3 H), 2.11 (s, 6 H), 4.22 (dd, J = 5.2, 14.7 Hz, 1 H), 4.34 (dd, J = 6.1, 14.7 Hz, 1 H), 5.11 (d, J = 8.3 Hz, 1 H), 7.23-7.31 (m, 5 H), 8.18 (d, J = 8.3 Hz, 1 H), 8.55 (br s, 1 H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.43, 40.33 (2 C), 42.28, 69.42, 126.73, 127.27 (2 C), 128.21 (2 C), 139.49, 168.49, 170.31 ppm.

2.0 IR (KBr) 3280, 1670 (br), 1500 (br), 1460, 760, 700 cm<sup>-1</sup>.

Mass spectrum (FD) 250 (M<sup>+</sup>+1).

Elemental analysis

Calculated for C<sub>13</sub>H<sub>19</sub>N<sub>3</sub>O<sub>2</sub> 62.63% C; 7.68% H; 16.85% N.

2.5 Found 62.82% C; 7.66% H; 16.69% N.

3.0

3.5

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EXAMPLE 55

1 Synthesis of 2-Acetamido-N-benzyl-2-(N-hydroxyamino)acetamide.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol),  
BBr<sub>3</sub> (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 8.8 mL, 8.8 mmol), and anhydrous NH<sub>2</sub>OH (5-6 equiv) gave  
5 an oily residue. The residue was separated into three components by flash  
chromatography on SiO<sub>2</sub> gel (7.5% MeOH/CHCl<sub>3</sub>).

2-Acetamido-N-benzyl-2-(N-hydroxyamino)acetamide.

Yield: 0.14 g (7%).

10 R<sub>f</sub> 0.30 (8% MeOH/CHCl<sub>3</sub>).

mp 144-146 °C (dec.) (recrystallized from EtOH)

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.88 (s, 3 H), 4.31 (d, J = 5.7 Hz, 2 H), 5.08 (dd, J = 4.4, 8.1 Hz,  
1 H), 5.94 (dd, J = 2.8, 4.4 Hz, 1 H), 7.19-7.35 (m, 5 H), 7.52 (d, J = 2.8 Hz, 1 H),  
15 8.26 (d, J = 8.1 Hz, 1 H), 8.42 (t, J = 5.7 Hz, 1 H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.69, 42.25, 67.86, 126.69, 127.14 (2 C), 128.18 (2 C), 139.08,  
168.53, 169.67 ppm.

20 IR (KBr) 3320 (br), 1660 (br), 1540 (br), 1460, 750, 700 cm<sup>-1</sup>.

Mass spectrum (FD) 238 (M<sup>++</sup> 1).

Elemental analysis

Calculated for C<sub>11</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub> 55.69% C; 6.37% H; 17.71% N.

25 Found 55.86% C; 6.37% H; 17.38% N.

Dimer A.

Yield: 0.05 g (3%).

R<sub>f</sub> 0.27 (8% MeOH/CHCl<sub>3</sub>).

30 mp 177-179 °C (recrystallized from EtOH).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.82 (s, 6 H), 4.25-4.34 (m, 4 H), 5.21 (d, J = 9.3 Hz, 2 H), 7.20-  
7.33 (m, 10 H), 8.16 (d, J = 9.3 Hz, 2 H), 8.26 (t, J = 5.8 Hz, 2 H), 8.51 (s, 1 H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.54 (2 C), 42.30 (2 C), 67.55 (2 C), 126.63 (2 C), 127.13 (4 C),  
35 128.11 (4 C), 139.02 (2 C), 168.24 (2 C), 169.33 (2 C) ppm.

IR (KBr) 3240 (br), 1640 (br), 1510 (br), 1450, 690 cm<sup>-1</sup>.

Mass spectrum (FD) 442 (M<sup>++</sup>+1).

1 Elemental analysis

Calculated for  $C_{22}H_{27}N_5O_5$  59.85% C; 6.16% H; 15.86% N.

Found 59.57% C; 6.08% H; 15.64% N.

5 Dimer B.

Yield: 0.10 g (6%).

$R_f$  0.18 (8% MeOH/ $CHCl_3$ ).

mp 184-186 °C (recrystallized from MeOH).

10  $^1H$  NMR ( $DMSO-d_6$ )  $\delta$  1.87 (6 H), 4.20 (dd,  $J = 5.3, 15.3$  Hz, 2 H), 4.44 (dd,  $J = 6.2, 15.3$  Hz, 2 H), 5.28 (d,  $J = 9.0$  Hz, 2 H), 7.15-7.31 (m, 10 H), 8.00 (d,  $J = 9.0$  Hz, 2 H), 8.39 (dd,  $J = 5.3, 6.2$  Hz, 2 H), 8.51 (s, 1 H).

15  $^{13}C$  NMR ( $DMSO-d_6$ ) 22.50 (2 C), 42.58 (2 C), 69.98 (2 C), 126.73 (2 C), 127.23 (4 C), 128.22 (4 C), 139.08 (2 C), 167.60 (2 C), 169.57 (2 C) ppm.

IR (KBr) 3300 (br), 1660 (br), 1530 (br), 1450, 740, 700  $cm^{-1}$ .

Mass spectrum (FD) 442 ( $M^{++1}$ ).

20 Elemental analysis

Calculated for  $C_{22}H_{27}N_5O_5$  59.85% C; 6.16% H; 15.86% N.

Found 60.09% C; 5.93% H; 15.76% N.

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EXAMPLE 56

1 Improved Synthesis of 2-Acetamido-N-benzyl-2-(N-hydroxyamino)acetamide.

2-Acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol) and BBr<sub>3</sub> (1 M in  
5 CH<sub>2</sub>Cl<sub>2</sub>, 17.2 mL, 17.2 mmol)) was dissolved in THF (250 mL), cooled (-10 °C), and then added dropwise (30 min) to a suspension of NH<sub>2</sub>OH (5-6 equiv) in THF (50 mL) at -10 °C. The reaction mixture was stirred (30 min) at this temperature and then allowed to warm to room temperature (1 h). The insoluble materials were  
10 filtered and the filtrate was concentrated in vacuo. The residue was separated into two components by flash column chromatography on SiO<sub>2</sub> gel (7.5% MeOH/CHCl<sub>3</sub>).

15 2-Acetamido-N-benzyl-2-(N-hydroxyamino)acetamide.

Yield: 0.66 g (23%).

mp 144-146 °C (dec.) (recrystallized from EtOH).

Dimer B.

20 Yield: 0.10 g (5%).

mp 184-186 °C (recrystallized from MeOH).

Dimer A was not observed under these conditions.

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EXAMPLE 57

1 Synthesis of 2-Acetamido-N-benzyl-2-(N<sup>2</sup>-phenylhydrazino)acetamide.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol),  
BBr<sub>3</sub> (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 10.0 mL, 10.0 mmol), and phenylhydrazine (2.60 g, 24.0  
5 mmol) gave a pale yellow oily residue which was purified by flash column  
chromatography on SiO<sub>2</sub> gel (2% MeOH/CHCl<sub>3</sub>) to give the desired product. The  
product was recrystallized from chloroform/hexane as a light yellow solid.

Yield: 0.75 g (29%).

10 R<sub>f</sub> 0.26 (2% MeOH/CHCl<sub>3</sub>).

mp 132-134 °C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.89 (s, 3 H), 4.28 (d, J = 5.8 Hz, 2 H), 4.89 (d, J = 5.2 Hz, 1 H),

5.09 (dd, J = 5.2, 7.4 Hz, 1 H), 6.61 (t, J = 7.4 Hz, 1 H), 6.70-7.28 (m, 10 H), 8.29

15 (d, J = 7.4 Hz, 1 H), 8.60 (t, J = 5.8 Hz, 1 H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.88, 42.22, 66.22, 112.66 (2 C), 117.57, 126.65, 127.08 (2 C),

128.15 (2 C), 128.53 (2 C), 139.12, 149.90, 168.66, 170.04 ppm.

20 IR (KBr) 3300, 1640 (br), 1610, 1520 (br), 1460, 760, 700 cm<sup>-1</sup>.

Mass spectra (FD) 313 (M<sup>+</sup>+1).

Elemental analysis

Calculated for C<sub>17</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub> 65.37% C; 6.45% H; 17.94% N.

25 Found 65.15% C; 6.25% H; 17.71% N.

EXAMPLE 58

1 Synthesis of 2-Acetamido-N-benzyl-2-(N<sup>2</sup>-benzyloxycarbonylhydrazino)acetamide.

Employing 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), BBr<sub>3</sub> (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 15.0 mL, 15.0 mmol), and benzyl carbazate (4.58 g, 27.6 mmol), 0.95 g (21%) of the desired product was obtained. The product was recrystallized from chloroform/hexane to give a white amorphous solid. R<sub>f</sub> 0.32 (2% MeOH/CHCl<sub>3</sub>).

mp 152-154 °C.

10 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.85 (s, 3 H), 4.27 (d, J = 4.4 Hz, 2 H), 5.00 (s, 2 H), 5.14 (dd, J = 3.1, 8.0 Hz, 1 H), 5.23 (t, J = 3.1 Hz, 1 H), 7.25-7.35 (m, 10 H), 8.26 (d, J = 8.0 Hz, 1 H), 8.56 (br s, 1 H), 8.66 (br s, 1 H).

15 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.71, 42.23, 65.56, 65.97, 126.69, 127.16 (2 C), 127.61 (2 C), 127.77, 128.13 (2 C), 128.27 (2 C), 136.74, 138.87, 168.04, 169.95 ppm.

IR (KBr) 3325, 1620 (br), 1500 (br), 1440, 740, 680 cm<sup>-1</sup>.

Mass spectrum (FD) 371 (M<sup>++</sup> 1).

20 Elemental analysis

Calculated for C<sub>19</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub> 61.61% C; 5.99% H; 15.13% N.

Found 61.40% C; 6.21% H; 15.39% N.



EXAMPLE 59

1 Synthesis of 2-Acetamido-N-benzyl-2-phenoxyacetamide.

Using 2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol),  
 BBr<sub>3</sub> (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 15.0 mL, 15.0 mmol), and NaOPh (4.18 g, 30 mmol) gave a  
 5 brown oily residue which was purified by flash column chromatography on SiO<sub>2</sub>  
 gel using first CHCl<sub>3</sub> and then 2% MeOH/CHCl<sub>3</sub> as the eluents to give the desired  
 product. The compound was recrystallized from chloroform/hexane.

Yield: 0.80 g (22%).

10 R<sub>f</sub> 0.58 (3% MeOH/CHCl<sub>3</sub>).

mp 125-128 °C (softens at 122 °C).

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.83 (s, 3 H), 4.35 (d, J = 5.7 Hz, 2 H), 6.18 (d, J = 9.4 Hz, 1 H),  
 6.94-6.99 (m, 2 H), 7.02-7.33 (m, 8 H), 8.98 (t, J = 5.7 Hz, 1 H), 9.10 (d, J = 9.4  
 15 Hz, 1 H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.54, 42.24, 76.44, 116.09 (2 C), 121.78, 126.84, 127.26 (2 C),  
 128.25 (2 C), 128.44 (2 C), 138.84, 155.97, 166.63, 170.73 ppm.

20 IR (KBr) 3300, 1650 (br), 1600, 1530 (br), 1490, 1450, 760, 700 cm<sup>-1</sup>.

Mass spectrum (FD) 299 (M<sup>+</sup>+1).

Elemental analysis

Calculated for C<sub>17</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>·0.5 H<sub>2</sub>O 66.43% C; 6.23% H; 9.11% N.

25 Found 66.62% C; 6.23% H; 9.16% N.

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EXAMPLE 60

1 Synthesis of 2-Acetamido-N-benzyl-2-(methylmercapto)acetamide.

A cooled (-78 °C) solution of Et<sub>3</sub>N (4.85 g, 48.0 mmol) in THF (20 mL) was added to a cooled (-78 °C) solution of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol) and BBr<sub>3</sub> (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 20.0 mL, 20.0 mmol)) in THF (275 mL). A cooled (-78 °C) solution of excess MeSH (5-6 equiv) in THF (55 mL) was then added. The reaction mixture was stirred at this temperature (30 min) and then at room temperature (1 h). The insoluble materials were filtered and the filtrate was evaporated to dryness in vacuo. The oily residue obtained was purified by flash column chromatography on SiO<sub>2</sub> gel (2% MeOH/CHCl<sub>3</sub>) to give 1.10 g (27%) of the desired product as a yellow orange oil. The product was purified by a second flash column chromatography on SiO<sub>2</sub> gel (2% MeOH/CHCl<sub>3</sub>) to give 0.72 g of the pure product as a white solid.

R<sub>f</sub> 0.65 (3% MeOH/CHCl<sub>3</sub>).

mp 155-157 °C.

<sup>1</sup>H NMR (CD<sub>3</sub>NO<sub>2</sub>) δ 1.98 (s, 3 H), 2.08 (s, 3 H), 4.39 (dd, J = 6.1, 15.2 Hz, 1 H), 4.49 (dd, J = 6.1, 15.2 Hz, 1 H), 5.51 (d, J = 7.8 Hz, 1 H), 7.15 (d, J = 7.8 Hz, 1 H), 7.17-7.41 (m, 6 H).

<sup>13</sup>C NMR (CD<sub>3</sub>NO<sub>2</sub>) 12.28, 22.94, 44.26, 56.03, 128.46, 128.60 (2 C), 129.77 (2 C), 140.17, 169.19, 171.06 ppm.

IR (KBr) 3320, 1650 (br), 1520 (br), 1460, 750 cm<sup>-1</sup>.

Mass spectrum (FD) 253 (M<sup>+</sup>+1).

Elemental analysis

Calculated for C <sub>12</sub> H <sub>16</sub> N <sub>2</sub> O <sub>2</sub> S	57.12% C;	6.39% H;	11.10% N.
Found	57.06% C;	6.57% H;	11.28% N.

EXAMPLE 611 Synthesis of 2-Acetamido-N-benzyl-2-(ethylmercapto)acetamide.

Using the procedure described for the synthesis of 2-acetamido-N-benzyl-2-(methylmercapto)acetamide, 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and EtSH (0.65 g, 10.4 mmol) were converted to 0.80 g (38%) of the desired product. The compound was further purified by recrystallization from chloroform/hexane to give a beige solid.

R<sub>f</sub> 0.60 (4% MeOH/CHCl<sub>3</sub>).

mp 146-148 °C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.56 (t, J = 7.4 Hz, 3 H), 1.88 (s, 3 H), 2.49-2.67 (m, 2 H), 4.23 (dd, J = 5.9, 15.2 Hz, 1 H), 4.32 (dd, J = 5.9, 15.2 Hz, 1 H), 5.55 (d, J = 9.1 Hz, 1 H), 7.20-7.35 (m, 5 H), 8.59 (d, J = 9.1 Hz, 1 H), 8.75 (t, J = 5.9 Hz, 1 H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 14.73, 22.43, 23.73, 42.10, 53.70, 126.87, 127.14 (2 C), 128.32 (2 C), 139.01, 167.89, 169.02 ppm.

IR (KBr) 3240, 1620 (br), 1510 (br), 1415, 680, 640 cm<sup>-1</sup>.

Mass spectrum (FD) 267 (M<sup>++</sup>1).

Elemental analysis

Calculated for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>2</sub>S·0.25 H<sub>2</sub>O

Found

57.65% C; 6.88% H; 10.34% N.

57.48% C; 6.84% H; 10.28% N.

1 Preparation of Functionalized  $\alpha$ -Heteroatom Substituted Amino Acids. General  
5 Procedure.

A mixture of 2-acetamido-2-(N,N,N-trimethylammonium)acetamide  
tetrafluoroborate (1 equiv), and the nitrogen nucleophile (4-5 equiv) in MeOH (1  
mmol/1 mL) was stirred at 55-60 °C (3 h). The solvent was removed in vacuo and  
the residue was purified by flash column chromatography on SiO<sub>2</sub> gel using the  
indicated solvents as the eluent.

10 Using this procedure the following examples were  
prepared.

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EXAMPL 621 Synthesis of 2-Acetamido-N-benzyl-2-(N-methoxyamino)acetamide.

Using a MeOH solution of MeONH<sub>2</sub> (prepared from MeONH<sub>2</sub>·HCl (2.83 g, 33.9 mmol) and NaOMe (1.41 g, 26.1 mmol)), and 2-acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (2.70 g, 7.67 mmol) gave an oily residue which was purified by flash column chromatography on SiO<sub>2</sub> gel (2% MeOH/CHCl<sub>3</sub>) to give the desired product. The product was recrystallized from chloroform/hexane.

10 Yield: 0.80 g (42%).

R<sub>f</sub> 0.23 (2% MeOH/CHCl<sub>3</sub>)

mp 95-97 °C.

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.88 (s, 3 H), 3.38 (s, 3 H), 4.22-4.41 (m, 2 H), 5.18 (dd, J = 4.9, 7.8 Hz, 1 H), 6.78 (d, J = 4.9 Hz, 1 H), 7.21-7.32 (m, 5 H), 8.33 (d, J = 7.8 Hz, 1 H), 8.56 (br s, 1 H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.64, 42.28, 61.42, 66.25, 126.74, 127.19 (2 C), 128.19 (2 C), 139.11, 167.95, 169.66 ppm.

20 IR (KBr) 3300, 1650, 1620, 1510 (br), 1440, 750, 680 cm<sup>-1</sup>.

Mass spectrum (FD) 252 (M<sup>++</sup>1).

Elemental analysis

25	Calculated for C <sub>12</sub> H <sub>17</sub> N <sub>3</sub> O <sub>3</sub>	57.63% C; 6.82% H; 16.72% N.
	Found	57.06% C; 6.63% H; 16.65% N.

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EXAMPLE 63

1 Synthesis of 2-Acetamido-N-benzyl-2-(N-(N-methylhydroxyamino))acetamide.

An MeOH solution (30 mL) of MeNHOH (21.74 mmol) (prepared from MeNHOH·HCl (2.36 g, 28.26 mmol) and NaOMe (1.17 g, 21.74 mmol)) and 2-  
 5 acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (2.20 g, 6.25 mmol) gave a residue which was purified by flash column chromatography on SiO<sub>2</sub> gel (6% MeOH/CHCl<sub>3</sub>) to give the desired product as a white solid. The product was then purified by recrystallization from EtOH.

10 Yield: 0.95 g (61%).

R<sub>f</sub> 0.32 (8% MeOH/CHCl<sub>3</sub>).

mp 159-161 °C.

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.95 (s, 3 H), 2.43 (s, 3 H), 4.26 (dd, J = 5.7, 15.1 Hz, 1 H), 4.35 (dd, J = 5.7, 15.1 Hz, 1 H), 5.09 (d, J = 9.1 Hz, 1 H), 7.21-7.29 (m, 5 H), 8.05 (s, 1 H), 8.18 (d, J = 9.1 Hz, 1 H), 8.23 (t, J = 5.7 Hz, 1 H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.40, 42.34, 43.92, 71.49, 126.62, 127.12 (2 C), 128.12 (2 C),  
 20 139.14, 167.82, 170.28 ppm.

IR (KBr) 3440 (br), 3300, 1640, 1530, 1460, 750, 700 cm<sup>-1</sup>.

Mass spectrum (FD) 252 (M<sup>++</sup>1).

Elemental analysis

25 Calculated for C<sub>12</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub> 57.36% C; 6.82% H; 16.72% N.  
 Found 57.65% C; 6.59% H; 16.66% N.

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EXAMPLE 64

1 Synthesis of 2-Acetamido-N-benzyl-2-(N-(N,O-dimethylhydroxyamino))acetamide.

An MeOH solution (20 mL) of MeNHOMe (17.39 mmol) (prepared from MeNHOMe·HCl (2.20 g, 23.02 mmol) and NaOMe (0.94 g, 17.39 mmol)) and 2-acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (2.10 g, 5.97 mmol) gave a solid residue. Flash column chromatography of the solid on SiO<sub>2</sub> gel (2% MeOH/CHCl<sub>3</sub>) yielded pure desired product. The product was recrystallized from EtOH.

10 Yield: 1.30 g (82%).

R<sub>f</sub> 0.39 (2% MeOH/CHCl<sub>3</sub>).

mp 165-167 °C.

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.93 (s, 3 H), 2.43 (s, 3 H), 3.32 (s, 3 H), 4.25 (dd, J = 5.9, 14.9 Hz, 1 H), 4.37 (dd, J = 5.9, 14.9 Hz, 1 H), 5.19 (d, J = 9.4 Hz, 1 H), 7.21-7.35 (m, 5 H), 8.31 (d, J = 9.4 Hz, 1 H), 8.56 (t, J = 5.9 Hz, 1 H).

<sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.36, 39.68, 42.34, 59.16, 70.33, 126.74, 127.41 (2 C), 128.21 (2 C), 139.30, 167.38, 170.30 ppm.

20 IR (KBr) 3300, 1640 (br), 1540 (br), 1460, 750, 700 cm<sup>-1</sup>.

Mass spectrum (FD) 266 (M<sup>++1</sup>).

Elemental analysis

25	Calculated for C <sub>13</sub> H <sub>19</sub> N <sub>3</sub> O <sub>3</sub>	58.85% C; 7.22% H; 15.84% N.
	Found	59.05% C; 7.37% H; 15.75% N.

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EXAMPLE 651 Synthesis of 2-Acetamido-N-benzyl-2-(N-isoxazolidino)acetamide.

Using 2-acetamido-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate (1.60 g, 4.55 mmol), isoxazolidine (prepared from isoxazolidine hydrobromide (2.41 g, 15.65 mmol) and NaOMe (0.70 g, 13.04 mmol)) gave the desired product. The product was recrystallized from chloroform/hexane to give a white amorphous solid.

Yield: 0.80 g (64%).

10  $R_f$  0.29 (4% MeOH/CHCl<sub>3</sub>).

mp 149-151 °C.

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.91 (s, 3 H), 2.05-2.20 (m, 2 H), 2.45-2.89 (m, 1 H), 2.98-3.07 (m, 1 H), 3.74-3.90 (m, 2 H), 4.25 (dd, J= 6.1, 15.3 Hz, 1 H), 4.35 (dd, J= 6.1, 15.3 Hz, 1 H), 5.23 (d, J= 9.2 Hz, 1 H), 7.15-7.35 (m, 5 H), 8.49 (d, J= 9.2 Hz, 1 H), 8.56 (br s, 1 H).

20 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.26, 28.26, 42.15, 48.94, 66.19, 68.77, 126.64, 127.02 (2 C), 128.13 (2 C), 139.22, 167.43, 170.27 ppm.

IR (KBr) 3400 (br), 3300, 1650, 1530, 1470, 740, 700, 610 cm<sup>-1</sup>.

Mass spectrum (FD) 278 (M<sup>+</sup>+1).

Elemental analysis

25 Calculated for C<sub>14</sub>H<sub>19</sub>N<sub>3</sub>O<sub>3</sub> 60.64% C; 6.91% H; 15.15% N.  
Found 60.16% C; 7.04% H; 15.07% N.

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1 Preparation of Functionalized  $\alpha$ -Heteroatom Substituted Amino Acids. General  
2 Procedure.

3 2-Acetamido-N-benzyl-2-ethoxyacetamide (1 equiv) was suspended in  
4 Et<sub>2</sub>O (100 mL/10 mmol), and then BF<sub>3</sub>·Et<sub>2</sub>O (1.6-2.4 equiv) was rapidly added and  
5 the resulting solution was stirred (10 min). The nucleophile (H<sub>2</sub>O or EtSH) (1.6-4.0  
6 equiv) was then added and the reaction was stirred at room temperature (18-48 h).  
7 The reaction was then quenched by the addition of an aqueous NaHCO<sub>3</sub> (100  
8 mL/10 mmol)/ice mixture. The experimental workup varied slightly for each  
9 compound and is described in the following examples along with  
10 the observed spectral properties.

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EXAMPLE 661 Synthesis of 2-Acetamido-N-benzyl-2-hydroxyacetamide.

Reacting 2-acetamido-N-benzyl-2-ethoxyacetamide (1.00 g, 4.0 mmol),  
BF<sub>3</sub>·Et<sub>2</sub>O (0.91 g, 6.4 mmol) and H<sub>2</sub>O (0.12 g, 6.7 mmol) followed by aqueous  
5 NaHCO<sub>3</sub> workup gave an aqueous reaction mixture. The solution was then  
extracted with EtOAc (3 X 50 mL), and the combined EtOAc extracts were dried  
(Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was purified by flash column  
10 chromatography on SiO<sub>2</sub> gel (3% MeOH/CHCl<sub>3</sub>) to give the desired product as a  
white solid.

Yield: 0.30 g (34%).

R<sub>f</sub> 0.14 (3% MeOH/CHCl<sub>3</sub>).

mp 136-138 °C.

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.85 (s, 3 H), 4.29 (d, J = 5.9 Hz, 2 H), 5.48 (dd, J = 5.5, 8.6 Hz,  
1 H), 6.47 (d, J = 5.5 Hz, 1 H), 7.21-7.35 (m, 5 H), 8.52 (t, J = 5.9 Hz, 1 H), 8.59  
(d, J = 8.6 Hz, 1 H).

20 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.66, 41.99, 71.42, 126.66, 127.22 (2 C), 128.13 (2 C), 139.20,  
169.47, 169.62 ppm.

IR (KBr) 3300, 1620, 1530 (br), 1430 (br), 730, 690 cm<sup>-1</sup>.

Mass spectrum, m/e (relative intensity) 223 (M<sup>+</sup>+1, 1), 163 (11), 134 (9), 106 (46), 91  
25 (100), 77 (22), 65 (38).

Elemental analysis

Calculated for C<sub>11</sub>H<sub>14</sub>N<sub>2</sub>O<sub>3</sub> 59.45% C; 6.35% H; 12.61% N.

Found 59.24% C; 6.36% H; 12.50% N.

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EXAMPLE 67

1 Synthesis of 2-Acetamido-N-benzyl-2-(ethylmercapto)acetamide.

5 Using 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol),  
BF<sub>3</sub>·Et<sub>2</sub>O (2.72 g, 19.2 mmol) and EtSH (2.38 g, 38.4 mmol) gave an aqueous  
10 reaction mixture. The solution was extracted with CHCl<sub>3</sub> (3 x 100 mL). The  
combined CHCl<sub>3</sub> layers were dried (Na<sub>2</sub>SO<sub>4</sub>), and then concentrated in vacuo to  
give the desired product as white solid.

Yield: 1.90 g (89%).

10 R<sub>f</sub> 0.60 (4% MeOH/CHCl<sub>3</sub>).

mp 148-149 °C (mixed melting point with an authentic sample of Example 61  
was undepressed).

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EXAMPLE 68

1 Synthesis of 2,2-Diacetamido-N-benzylacetamide.

5 Ac<sub>2</sub>O (1 mL) was added to a solution of 2-acetamido-N-benzyl-2-aminoacetamide (1.10 g, 4.98 mmol) in dry pyridine (10 mL) and then CH<sub>2</sub>Cl<sub>2</sub> (20 mL) was added. The mixture was stirred at room temperature (4 h) and then the volatile materials were removed in vacuo. The residue was then treated with a saturated aqueous NaHCO<sub>3</sub> solution (50 mL). The white solid that remained was the desired product and was filtered, dried (Na<sub>2</sub>SO<sub>4</sub>), and recrystallized from 10 MeOH.

Yield: 1.20 g (92%).

mp 265-267 °C (dec.).

15 <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.84 (s, 6 H), 4.26 (d, J = 5.8 Hz, 2 H), 5.71 (t, J = 7.6 Hz, 1 H), 7.20-7.31 (m, 5 H), 8.44 (d, J = 7.6 Hz, 2 H), 8.48 (t, J = 5.8 Hz, 1 H).

<sup>13</sup>C (DMSO-d<sub>6</sub>) 22.44 (2 C), 42.26, 56.99, 126.62, 127.02 (2 C), 128.12 (2 C), 139.15, 168.19, 169.39 (2 C) ppm.

20 IR (KBr) 3260, 1530, 1500, 740, 690 cm<sup>-1</sup>.

Mass spectrum (FD) 264 (M<sup>++</sup>1).

Elemental analysis

Calculated for C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>

Found

59.30% C;	6.51%H;	15.96% N.
59.16% C;	6.49%H;	15.86% N.

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EXAMPLE 69Synthesis of 2-Acetamido-N-benzyl-2-trifluoroacetamidoacetamide.

Ice cold trifluoroacetic anhydride (8 mL) was added in one portion to ice cold 2-acetamido-N-benzyl-2-aminoacetamide (1.00 g, 4.53 mmol). The reaction was accompanied by the evolution of heat. After stirring (5 min), the volatile materials were removed in vacuo. The residue was treated with a saturated aqueous  $\text{NaHCO}_3$  solution (20 mL), and the solid that remained was filtered and washed with  $\text{H}_2\text{O}$  to give the desired product. The product was recrystallized from EtOH.

Yield: 1.00 g (70%).

$R_f$  0.34 (8% MeOH/ $\text{CHCl}_3$ ).

mp 228-230 °C.

$^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.90 (s, 3 H), 4.30 (d,  $J = 5.1$  Hz, 2 H), 5.85 (d,  $J = 8.0$  Hz, 1 H), 7.21-7.35 (m, 5 H), 8.64 (d,  $J = 8.0$  Hz, 1 H), 8.75 (t,  $J = 5.1$  Hz, 1 H), 10.04 (s, 1 H).

$^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ) 22.52, 42.52, 57.42, 117.4 (q,  $\text{JCF} = 288.3$  Hz), 126.80, 127.16 (2 C), 128.21 (2 C), 138.93, 156.14 (q,  $\text{JCF} = 35.3$  Hz), 166.39, 169.88 ppm.

IR (KBr) 3300, 1720, 1660, 1520, 1380, 760, 700  $\text{cm}^{-1}$ .

Mass spectrum (FD) 318 ( $\text{M}^{++} 1$ ).

Elemental analysis

Calculated for $\text{C}_{13}\text{H}_{14}\text{N}_3\text{O}_3\text{F}_3$	49.21% C;	4.45% H;	13.24% N.
Found	49.48% C;	4.43% H;	13.10% N.

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EXAMPLE 70

1 Synthesis of 2-Acetamido-N-benzyl-2-(N,N,N-trimethylammonium)acetamide  
Tetrafluoroborate.

5 A solution of 2-acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide  
 (1.93 g, 7.76 mmol) in nitromethane (7 mL) was added slowly to an ice cold  
 solution of trimethyloxonium tetrafluoroborate (1.26 g, 8.54 mmol) in nitro-  
 methane (6 mL). The reaction mixture was stirred at this temperature (15 min)  
 and then at room temperature (2 h). Anhydrous Et<sub>2</sub>O (~50 mL) was added to the  
 10 reaction mixture and the white solid that separated was filtered, washed with  
 Et<sub>2</sub>O, and dried in vacuo.

Yield: 1.95 g (72%).

mp 171-173 °C (dec.).

15 <sup>1</sup>H NMR (CD<sub>3</sub>NO<sub>2</sub>) δ 2.14 (s, 3 H), 3.18 (s, 9 H), 4.50 (d, J = 5.8 Hz, 2 H), 5.70 (d, J =  
 9.3 Hz, 1 H), 7.30-7.41 (m, 5 H), 7.57 (d, J = 9.3 Hz, 1 H), 7.70 (br s, 1 H).

IR (KBr) 3300, 1680 (br), 1530, 1490, 710 cm<sup>-1</sup>.

20 Mass spectrum (FD) 264 (M<sup>+</sup>).

Elemental analysis

Calculated for C<sub>14</sub>H<sub>22</sub>N<sub>3</sub>O<sub>2</sub>BF<sub>4</sub> 47.89% C; 6.31% H; 11.97% N.

Found 47.80% C; 6.33% H; 12.00% N.

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EXAMPLE 711 Synthesis of 2-Acetamido-N-benzyl-2-(ethylmercapto)acetamide-S-oxide.

5 A solution of *m*-chloroperbenzoic acid (1.00 g (~65%), 3.76 mmol) in CH<sub>2</sub>Cl<sub>2</sub> (10 mL) was added dropwise into a stirred, cooled (-10 to -15 °C) CH<sub>2</sub>Cl<sub>2</sub> solution (125 mL) of 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide (1.00 g, 3.76 mmol) under N<sub>2</sub>. The reaction was stirred (30 min) at this temperature and then the *m*-chlorobenzoic acid was precipitated as its ammonium salt by passing NH<sub>3</sub> gas over the surface of the reaction solution. The excess NH<sub>3</sub> was removed by  
 10 passing N<sub>2</sub> gas through the solution (20 min) at room temperature. The ammonium salt was filtered, and the filtrate was concentrated in vacuo. The residue was purified by flash chromatography on SiO<sub>2</sub> gel (2% MeOH/CHCl<sub>3</sub>) to give the desired product. The product was recrystallized from chloroform/hexane  
 15 as a white granular solid.

Yield: 0.55 g (52%).

R<sub>f</sub> 0.23 (2% MeOH/CHCl<sub>3</sub>).

20 mp 135-137 °C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.15 (t, J = 7.5 Hz, 3 H), 1.99 (s, 3 H), 2.49-2.56 (m, 1 H), 2.65-2.72 (m, 1 H), 4.34 (d, J = 5.7 Hz, 2 H), 5.55 (d, J = 9.5 Hz, 1 H), 7.23-7.34 (m, 5 H), 8.74 (d, J = 9.5 Hz, 1 H), 8.77 (t, J = 5.7 Hz, 1 H).

25 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 7.03, 22.34, 42.40, 42.47, 67.15, 126.89, 127.27 (2 C), 128.24 (2 C), 138.55, 164.66, 170.18 ppm.

IR (KBr) 3300 (br), 1640 (br), 1510 (br), 1370, 1230, 1100, 1020, 900 cm<sup>-1</sup>.

Mass spectrum (FD) 283 (M<sup>++1</sup>).

30 Elemental analysis

Calculated for C <sub>13</sub> H <sub>18</sub> N <sub>2</sub> O <sub>3</sub> S	55.30% C; 6.43% H; 9.92% N.
Found	55.17% C; 6.38% H; 9.70% N.

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## EXAMPLE 72

1 Synthesis of 2-Acetamido-N-benzyl-2-(S-ethylmercapto)acetamide-S-oxide.

A solution of  $\text{NaIO}_4$  (1.77 g, 8.27 mmol) in  $\text{H}_2\text{O}$  (20 mL) was added dropwise into a stirred solution of 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide (2.00 g, 7.52 mmol) in MeOH (25 mL). A precipitate appeared rapidly.  $\text{H}_2\text{O}$  (~30 mL) was added to the mixture to dissolve most of the suspension, and the reaction was stirred (4 h) at room temperature. The reaction was concentrated in vacuo and the remaining aqueous mixture was extracted with  $\text{CHCl}_3$  (3 x 100 mL). The combined  $\text{CHCl}_3$  extracts were dried ( $\text{Na}_2\text{SO}_4$ ) and the solvent was removed in vacuo. The oily residue (1.95 g, 92%) solidified on drying in vacuo. NMR analysis ( $\text{DMSO-d}_6$ ) of the product showed that it was a 2:1 mixture of the two diastereomers of the desired product. The reaction was recrystallized from EtOAc to give nearly pure diastereomer A (1.20 g) that was obtained from the m-chloroperbenzoic acid reaction. The EtOAc mother liquor was concentrated and the remaining residue (0.75 g) was recrystallized from ethyl acetate/hexane to give a diastereomeric mixture (0.41 g) of the two diastereomers A and B in a 2:3 ratio, respectively.

$R_f$  0.60 (4% MeOH/ $\text{CHCl}_3$ ).

mp 135-137 °C (softens at 117 °C).

25 IR (KBr) 3300 (br), 1640 (br), 1510 (br), 1370, 1230, 1100, 1020, 900  $\text{cm}^{-1}$ .

Mass spectrum (FD) 283 ( $\text{M}^++1$ ).

Elemental analysis: Calculated for  $\text{C}_{13}\text{H}_{18}\text{N}_2\text{O}_3\text{S}$ : 55.30% C; 6.43% H; 9.92% N.

Found: 55.58% C; 6.49% H; 9.97% N.

30 The following NMR spectral properties have been assigned to compounds A and B.

Diastereomer A.

35  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  1.16 (t,  $J = 7.5$  Hz, 3 H), 2.00 (s, 3 H), 2.49-2.72 (m, 2 H), 4.28-4.39 (m, 2 H), 5.56 (d,  $J = 9.7$  Hz, 1 H), 7.21-7.34 (m, 5 H), 8.71-8.77 (m, 2 H).

$^{13}\text{C}$  NMR ( $\text{DMSO-d}_6$ ) 7.10, 22.43, 42.48, 42.57, 67.23, 126.98, 127.36 (2 C), 128.33 (2 C), 138.63, 164.73, 170.25 ppm.

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1 Diastereomer B.

$^1\text{H}$  NMR (DMSO- $d_6$ )  $\delta$  1.13 (t,  $J = 7.6$  Hz, 3 H), 1.94 (s, 3 H), 2.49-2.72 (m, 2 H), 4.28-4.39 (m, 2 H), 5.71 (d,  $J = 9.9$  Hz, 1 H), 7.21-7.34 (m, 5 H), 8.83 (d,  $J = 9.9$  Hz, 1 H), 8.98 (t,  $J = 5.6$  Hz, 1 H).

5  $^{13}\text{C}$  NMR (DMSO- $d_6$ ) 6.47, 22.43, 41.53, 42.55, 67.90, 126.98, 127.36 (2 C), 128.33 (2 C), 138.39, 164.43, 169.82 ppm.

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EXAMPLE 731 Synthesis of 2-Acetamido-N-benzyl-2-(ethanesulfonyl)acetamide.

An aqueous solution (20 mL) of NaIO<sub>4</sub> (3.00 g, 14.02 mmol) was added to a MeOH solution (20 mL) of 2-acetamido-N-benzyl-2-(ethylmercapto)acetamide  
5 (0.95 g, 3.57 mmol). The initial homogeneous solution rapidly became turbid. H<sub>2</sub>O (~10 mL) was then added dropwise until the system became homogeneous. The solution was stirred (18 h) at 50-60 °C. MeOH (50 mL) was added to the reaction solution and the precipitated salt was filtered and washed with MeOH (10  
10 mL). The filtrate was concentrated and the remaining solution was extracted with CHCl<sub>3</sub> (3 x 50 mL). The combined CHCl<sub>3</sub> extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated in vacuo. The residue was purified by flash chromatography on SiO<sub>2</sub> gel (1% MeOH/CHCl<sub>3</sub>) to give the desired product. The product was further  
15 purified by recrystallization from EtOH:.

Yield: 0.34 g (32%).

R<sub>f</sub> 0.34 (3% MeOH/CHCl<sub>3</sub>).

20 mp 161-163 °C.

<sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.22 (t, J = 7.4 Hz, 3 H), 1.99 (s, 3 H), 3.04-3.24 (m, 2 H), 4.31 (dd, J = 5.7, 15.3 Hz, 1 H), 4.41 (dd, J = 5.7, 15.3 Hz, 1 H), 5.93 (d, J = 9.8 Hz, 1 H), 7.22-7.35 (m, 5 H), 9.13 (t, J = 5.7 Hz, 1 H), 9.17 (d, J = 9.8 Hz, 1 H).

25 <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 5.72, 22.27, 42.63, 45.43, 69.14, 127.02, 127.28 (2 C), 128.33 (2 C), 138.16, 161.88, 169.83 ppm.

IR (KBr) 3300, 2940, 1660, 1520, 1310, 1230, 1120, 900 cm<sup>-1</sup>.

Mass spectrum (FD) 298 (M<sup>+</sup>).

30 Elemental analysis

Calculated for C<sub>13</sub>H<sub>18</sub>N<sub>2</sub>O<sub>4</sub>S 52.33% C; 6.08% H; 9.39% N.

Found 52.52% C; 6.06% H; 9.53% N.

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EXAMPLE 74

1 Synthesis of 2-Acetamido-N-benzyl-2-(N,N,N-trimethylammonium)acetamide  
5 Tetrafluoroborate.

A solution of 2-acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide  
(1.93 g, 7.76 mmol) in nitromethane (7 mL) was added slowly to an ice cold  
solution of trimethyloxonium tetrafluoroborate (1.26 g, 8.54 mmol) in nitro-  
methane (6 mL). The reaction mixture was stirred at this temperature (15 min)  
and then at room temperature (2 h). Anhydrous Et<sub>2</sub>O (~50 mL) was added to the  
reaction mixture and the white solid that separated was filtered, washed with  
Et<sub>2</sub>O, and dried in vacuo.

Yield: 1.95 g (72%).

mp 171-173 °C (dec.).

<sup>1</sup>H NMR (CD<sub>3</sub>NO<sub>2</sub>) δ 2.14 (s, 3 H), 3.18 (s, 9 H), 4.50 (d, J = 5.8 Hz, 2 H), 5.70 (d, J =  
9.3 Hz, 1 H), 7.30-7.41 (m, 5 H), 7.57 (d, J = 9.3 Hz, 1 H), 7.70 (br s, 1 H).

IR (KBr) 3300, 1680 (br), 1530, 1490, 710 cm<sup>-1</sup>.

Mass spectrum (FD) 264 (M<sup>+</sup>).

Elemental analysis

Calculated for C<sub>14</sub>H<sub>22</sub>N<sub>3</sub>O<sub>2</sub>BF<sub>4</sub> 47.89% C; 6.31% H; 11.97% N.

Found 47.80% C; 6.33% H; 12.00% N.

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Example 75

1        *Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrrole)acetamide.* A solution of 2-  
acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-  
ethoxyacetamide (2.00 g, 8.0 mmol) and BBr<sub>3</sub> (1 M CH<sub>2</sub>Cl<sub>2</sub> solution, 8.8 mL, 8.8  
5 mmol)) was prepared in THF (225 mL) and cooled to -78 °C. It was then added  
under N<sub>2</sub> gas atmosphere to a cooled (-78 °C) suspension of potassium pyrrole  
(2.71 g, 25.8 mmol) in THF (25 mL). The reaction mixture was stirred at -78 °C (1  
h) and then at room temperature (1 h). It was then treated with water (10 mL)  
10 and acidified with 5% citric acid to pH 4.0 after which it was made basic with  
aqueous saturated Na<sub>2</sub>CO<sub>3</sub> solution. The aqueous mixture was extracted with  
EtOAc (2 x 250 mL) and the organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>). The volatile  
15 materials were removed *in vacuo* and the residue was purified by flash column  
chromatography on silica gel using 3% MeOH/CHCl<sub>3</sub> as the eluant to give 0.4 g  
(18%) of the desired product. It was purified by recrystallization from EtOH: mp  
182-184 °C; R<sub>f</sub> 0.44 (4% MeOH/CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.91 (s, COCH<sub>3</sub>), 4.30  
20 (d, *J* = 5.5 Hz, CH<sub>2</sub>), 6.01 (s, 2 x C<sub>3</sub>H), 6.38 (d, *J* = 8.7 Hz, CH), 6.85 (s, 2 x C<sub>2</sub>H), 7.11-  
7.35 (m, 5PhH), 8.96 (t, *J* = 5.5 Hz, NH), 9.14 (d, *J* = 8.7 Hz, NH); <sup>13</sup>C NMR (DMSO-  
d<sub>6</sub>) 22.22 (COCH<sub>3</sub>), 42.15 (CH<sub>2</sub>), 62.86 (CH), 107.79 (2C<sub>3</sub>), 119.19 (2C<sub>2</sub>), 126.76 (C<sub>4</sub>),  
127.01 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.11 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 138.34 (C<sub>1'</sub>), 166.37 (CONH), 169.41  
25 (COCH<sub>3</sub>) ppm; mass spectrum, *m/e* (relative intensity) 272 (M<sup>++1</sup>, 22), 271 (M<sup>+</sup>,  
100).

Anal. Calcd for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>·0.2 H<sub>2</sub>O: C, 65.53; H, 6.37; N, 15.28. Found: C,  
65.80; H, 6.22; N, 15.13.

Example 76

1        *Synthesis of 2-Acetamido-N-benzyl-2-(1-imidazole)acetamide.* Making use  
of the experimental procedure described in the above experiment, 2-acetamido-N-  
5        benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol), BBr<sub>3</sub> (1 M CH<sub>2</sub>Cl<sub>2</sub> solution, 8.8 mL,  
8.8 mmol), Et<sub>3</sub>N (1.62 g, 1.60 mmol), and imidazole (0.60 g, 8.8 mmol) gave 0.60 g  
(30%) of the desired product. It was recrystallized from ethyl acetate/hexane as a  
beige colored solid: mp 146-148 °C; R<sub>f</sub> 0. (7% MeOH/CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ  
10        1.85 (s, COCH<sub>3</sub>), 4.30 (br s, CH<sub>2</sub>), 6.53 (d, *J* = 8.0 Hz, CH), 6.89 (s, C<sub>5</sub>H), 7.12-7.33  
(m, C<sub>4</sub>H, 5PhH), 7.69 (s, C<sub>2</sub>H), 9.06 (br s, NH), 9.29 (d, *J* = 8.0 Hz, NH); <sup>13</sup>C NMR  
(DMSO-d<sub>6</sub>) 22.28 (COCH<sub>3</sub>), 42.36 (CH<sub>2</sub>), 61.18 (CH), 117.56 (C<sub>5</sub>), 126.92 (C<sub>4</sub>), 127.16  
(2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.19 (C<sub>4</sub>), 128.26 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 136.21 (C<sub>2</sub>), 138.27 (C<sub>1</sub>), 165.72  
15        (CONH), 169.77 (COCH<sub>3</sub>) ppm; mass spectrum, FD (relative intensity) 274 (M<sup>+</sup>+2,  
12), 273 (M<sup>+</sup>+1, 77), 272 (100), 205 (34), 274 (18).

Anal. Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95;  
H, 6.09; N, 20.32.

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Example 77

1        *Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrazole)acetamide.* A solution of 2-  
acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-  
ethoxyacetamide (3.60 g, 14.4 mmol) and  $\text{BBr}_3$  (1 M  $\text{CH}_2\text{Cl}_2$  solution, 15.8 mL, 15.8  
5 mmol)) was prepared in THF (250 mL) and cooled to  $-78^\circ\text{C}$ . A solution of  
triethylamine (2.91 g, 28.8 mmol) in THF (20 mL) was then added to the above  
solution. This was followed by the addition of THF (30 mL) solution of pyrazole  
10 (1.17 g, 17.28 mmol) and the mixture thus obtained was stirred at  $-78^\circ\text{C}$  (30 min)  
and room temperature (1 h). The insoluble materials were filtered and the  
solvents removed from the filtrate *in vacuo*. The residue was then purified by  
flash column chromatography on silica gel using 4%  $\text{MeOH}/\text{CHCl}_3$  as the eluant  
15 to give 0.80 g (22%) of the desired product. It was then recrystallized from EtOAc  
as a white solid: mp  $158-160^\circ\text{C}$ ;  $R_f$  0.51 (6%  $\text{MeOH}/\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$   
1.93 (s,  $\text{COCH}_3$ ), 4.29 (d,  $J = 5.8$  Hz, NH), 6.26 (s,  $\text{C}_4\text{H}$ ), 6.57 (d,  $J = 8.8$  Hz, CH),  
7.15-7.33 (m, 5PhH), 7.48 (br s,  $\text{C}_5\text{H}$ ), 7.76 (br s,  $\text{C}_3\text{H}$ ), 8.96 (t,  $J = 5.8$  Hz, NH), 9.23  
20 (d,  $J = 8.8$  Hz, NH);  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ) 22.41 ( $\text{COCH}_3$ ), 42.40 ( $\text{CH}_2$ ), 65.51 (CH),  
105.37 ( $\text{C}_4$ ), 126.87 ( $\text{C}_4'$ ), 127.14 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ), 128.25 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ), 129.00 ( $\text{C}_5$ ),  
138.59 ( $\text{C}_3$ ), 139.17 ( $\text{C}_1'$ ), 165.68 (CONH), 169.81 ( $\text{COCH}_3$ ) ppm; mass spectrum,  $m/e$   
(relative intensity) 273 ( $\text{M}^{++1}$ , 11), 272 ( $\text{M}^+$ , 2), 139 (83), 138 (100), 92 (37).

25        Anal. Calcd for  $\text{C}_{14}\text{H}_{16}\text{N}_4\text{O}_2$ : C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95;  
H, 5.96; N, 20.28.

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Example 78

1        *Synthesis of 2-Acetamido-N-benzyl-2-(1-(1,2,4-triazole))acetamide.* Using 2-  
acetamido-N-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol), BBr<sub>3</sub> (1 M CH<sub>2</sub>Cl<sub>2</sub>  
solution, 17.6 mL, 17.6 mmol), Et<sub>3</sub>N (4.85 g, 48.0 mmol), and 1,2,4-triazole (1.43 g,  
5   20.8 mmol), 1.20 g (28%) of the desired product was obtained. It was recrystallized  
from EtOAc as an amorphous white solid: mp 146-148 °C; R<sub>f</sub> 0.48 (6% MeOH/  
CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.85 (s, COCH<sub>3</sub>), 4.32 (br s, CH<sub>2</sub>), 6.70 (d, J = 7.8 Hz,  
CH), 7.21-7.29 (m, 5PhH), 8.01 (s, C<sub>3</sub>H), 8.57 (s, C<sub>5</sub>H), 9.04 (br s, NH), 9.39 (d, J = 7.8  
10 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.39 (COCH<sub>3</sub>), 42.59 (CH<sub>2</sub>), 65.02 (CH), 126.97 (C<sub>4</sub>'),  
127.25 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.32 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 138.47 (C<sub>1</sub>'), 143.93 (C<sub>5</sub>), 151.50 (C<sub>3</sub>),  
164.77 (CONH), 170.23 (COCH<sub>3</sub>) ppm; mass spectrum, FD (relative intensity) 275  
(M<sup>++2</sup>, 12), 274 (M<sup>++1</sup>, 100), 273 (11), 205 (19), 204 (13), 140 (67), 139 (31).

15        Anal. Calcd for C<sub>13</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub>: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.37;  
H, 5.66; N, 25.38.

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Example 79

1        *Synthesis of 2-Acetamido-N-benzyl-2-(1-tetrazole)acetamide.* Making use of  
2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), BBr<sub>3</sub> (1 M CH<sub>2</sub>Cl<sub>2</sub>  
5 solution, 13.2 mL, 13.2 mmol), Et<sub>3</sub>N (2.42 g, 24.0 mmol), and tetrazole (1.10 g, 15.6  
mmol), 0.90 g (27%) of the desired product was obtained as a white solid. It was  
recrystallized from EtOH: mp 169-171 °C; R<sub>f</sub> 0.22 (4% MeOH/CHCl<sub>3</sub>); <sup>1</sup>H NMR  
(DMSO-d<sub>6</sub>) δ 1.97 (s, COCH<sub>3</sub>), 4.25-4.40 (m, CH<sub>2</sub>), 7.05 (d, J = 8.4 Hz, CH), 7.21-7.38  
(m, 5PhH), 9.23 (t, J = 5.5 Hz, NH), 9.44 (s, C<sub>5</sub>H), 9.69 (d, J = 8.4 Hz, NH); <sup>13</sup>C NMR  
10 (DMSO-d<sub>6</sub>) 22.38 (COCH<sub>3</sub>), 42.78 (CH<sub>2</sub>), 63.62 (CH), 127.10 (C<sub>4</sub>'), 127.39 (2C<sub>2</sub>' or  
2C<sub>3</sub>'), 128.38 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 138.26 (C<sub>1</sub>'), 143.67 (C<sub>5</sub>), 163.88 (CONH), 170.62 (COCH<sub>3</sub>)  
ppm; mass spectrum, FD (relative intensity) 275 (M<sup>+</sup> 79), 273 (14), 206 (100), 205  
(50).

15        Anal. Calcd for C<sub>12</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>: C, 52.55; H, 5.15; N, 30.64. Found: C, 52.75;  
H, 5.33; N, 30.64.

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Example 80

1 Preparation of  $\alpha$ -acetamido-N-benzyl-2-pyridylacetamide and 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide.

5 Preparation of 2-acetamido-2-bromo-N-benzylacetamide.

A solution of 2-acetamido-2-ethoxy-N-benzylacetamide (2.00 g, 8 mmol) in dry  $\text{CH}_2\text{Cl}_2$  (200 mL) was stirred at room temperature as a solution of  $\text{BBr}_3$  (8.8 mL, 8.8 mmol, 1.0 M in  $\text{CH}_2\text{Cl}_2$ ) was introduced by means of a syringe under a nitrogen atmosphere. A white mist formed and after it disappeared, the  $\text{N}_2$  line was removed and the reaction sealed. The resulting yellow solution was stirred (3.5 h) and then concentrated in vacuo to give yellow crystals of  $\alpha$ -acetamido-2-bromo-N-benzyl acetamido which was stored under vacuum overnight.

Preparation of 2-pyridyllithium.

20 The generation of 2-pyridyllithium in situ was run under nitrogen. A solution of n-butyllithium (7.2 mL, 2.5 M solution in hexane, 18 mmol) was added to dry ether (60 mL), cooled to  $-20^\circ\text{C}$ , and stirred as 2-bromopyridine (1.6 mL, 17 mmol) in dry ether (15 mL) was added dropwise (15 min). The resulting blood red solution was stirred at  $-20^\circ\text{C}$  for an additional 5 minutes and then transferred through a doubled-ended needle under a stream of nitrogen to an addition funnel where it was cooled to  $-78^\circ\text{C}$ .

30 Preparation of  $\alpha$ -acetamido-N-benzyl-2-pyridylacetamide and 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide.

The cooled 2-pyridyllithium solution was added dropwise (approximately 2 drops per second) to the solution of 2-acetamido-2-bromo-N-benzylacetamide in dry THF (200 mL) and maintained at  $-78^\circ\text{C}$ . The reaction mixture was stirred for an additional 30-45 minutes at  $-78^\circ\text{C}$ . The reaction was quenched with saturated aqueous solution of  $\text{NH}_4\text{Cl}$  (40 mL) at  $-78^\circ\text{C}$  producing a heterogenous mixture

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1  $\text{Na}_2\text{CO}_3$  was added dropwise until the precipitate dissolved. The organic layer  
 was separated and then the aqueous layer was extracted with ether (2 x 50 mL).  
 The combined organic layers were dried ( $\text{Na}_2\text{SO}_4$ ), concentrated under vacuum  
 5 and separated using flash chromatography on silica gel with ethyl acetate as the  
 eluent. The fractions containing the products were concentrated under vacuum,  
 separated and then further purified by column chromatography on alumina  
 (80-200 mesh, Grade 1, Fisher) employing ethyl acetate as the solvent. Fractions  
 10 containing  $\alpha$ -acetamido-N-benzyl-2-pyridylacetamide was concentrated to dryness  
 and gave a white amorphous solid (250 mg, 11% yield);  $R_f = 0.39$  (5%  
 $\text{CH}_3\text{OH}/\text{CHCl}_3$ ); mp 146-147 °C; IR (KBr) 3290, 3180, 3020, 1620 br, 1580, 1520 br,  
 1480, 1420, 1370, 1310, 1260  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.96 (s, 3H), 4.28  
 15 (d,  $J = 5.8$  Hz, 2H), 5.59 (d,  $J = 8.0$  Hz, 1H), 7.18 -7.30 (m, 5H), 7.32 (dd,  $J = 7.7, 5.2$   
 Hz, 1H), 7.47 (d,  $J = 7.7$  Hz, 1H), 7.80 (dt,  $J = 7.7, 1.5$  Hz, 1H), 8.55 (m, 2H), 8.78 (br  
 t,  $J = 5.8$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  $\text{DMSO}-d_6$ ) 22.5, 42.1, 58.3, 121.7, 122.8, 126.6,  
 126.9 (2C), 128.1 (2C), 136.8, 139.1, 148.6, 157.2, 169.0, 169.2 ppm; FD (Lilly) mass  
 20 spectrum,  $m/e$  (relative intensity) 284 ( $M^+ + 1$ , 6), 283 ( $M^+$ , 0.8), 151 (8), 150 (100),  
 141 (4).  $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_2$

Anal. Calcd for  $\text{C}_{16}\text{H}_{17}\text{N}_3\text{O}_2$ , C 67.83, H, 6.05, N, 14.83

Found: C, 68.11, H, 6.00, N, 14.89.

25 Fractions containing 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide were  
 combined, concentrated in vacuo and yielded a white amorphous solid: (150 mg,  
 6% yield).  $R_f$  0.34 (5%  $\text{CH}_3\text{OH}/\text{CHCl}_3$ ); mp 226 decomposed (recrystallized in  
 ethanol)  $^1\text{H}$  NMR (300 MHz,  $\text{DMSO}-d_6$ )  $\delta$  1.94 s, 4.26 (dd,  $J = 15.2, 5.7$  Hz, 1H), 4.33  
 30 (dd,  $J = 15.2, 6.1$  Hz, 1H), 6.26 (br t,  $J = 6.8$  Hz, 1H), 6.37 (br d,  $J = 9.1$  Hz, 1H), 6.69 (d,  
 $J = 8.7$  Hz, 1H), 7.22-7.33 (m, 5H), 7.42 (ddd,  $J = 9.1, 6.8, 1.6$  Hz, 1H), 7.58 (dd,  $J = 6.8,$   
 35 1.6 Hz, 1H), 8.93 (br t,  $J = 5.8$  Hz, 1H), 9.20 (d,  $J = 8.7$  Hz, 1H);  $^{13}\text{C}$  NMR (75 MHz,  
 $\text{DMSO}-d_6$ ) 22.5, 42.5, 62.5, 105.1, 119.4, 126.80, 127.10 (2C), 128.2 (2C), 135.6, 138.8,  
 140.2, 161.2, 166.0, 170.0 ppm. Hydrogen and carbon assignments were verified  
 with  $^1\text{H}-^1\text{H}$  COSY,  $^1\text{H}-^{13}\text{C}$ -COSY, zero quantum NMR experiments. The  
 structure was confirmed by X-ray crystallography.

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1 Preparation of authentic 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide.

The generation of 2-hydroxypyridylsodium *in situ* was done under anhydrous conditions. A solution of 2-hydroxypyridine (1.57 g, 16 mmol, vacuum dried, 97% Aldrich) in dry THF (200 mL) was stirred and cooled to 0°C and then NaH (0.77 g, 60% in mineral oil, 19.2 mmol) was added in one portion leading to the evolution of H<sub>2</sub> and the generation of a heterogeneous mixture. A solution of 2-acetamido-2-bromo-N-benzylacetamide (8 mmol based on 2-acetamido-2-ethoxy-N-benzylacetamide) in dry THF (160 mL) was then transferred through a double-ended needle by means of a stream of nitrogen. The resulting mixture was quenched with saturated aqueous solution of NH<sub>4</sub>Cl (50 mL) at 0°C producing a white precipitate. A saturated aqueous solution Na<sub>2</sub>CO<sub>3</sub> was added dropwise while stirring at 0°C until all of the white precipitate dissolved. The two layers were separated while cold and then the aqueous fraction was extracted with THF (2 x 100 mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), and concentrated to dryness. The crude reaction mixture residue was dissolved in a minimum of CHCl<sub>3</sub> and was flash chromatographed on a silica gel column using ethyl acetate as the eluent and gave a white amorphous solid (1.10 g, 46% yield) which was identical to properties previously observed for 2-acetamido-N-benzyl-2-(2'-pyridone)acetamide: R<sub>f</sub> 0.34 (5% CH<sub>3</sub>OH/CHCl<sub>3</sub>); mp 162-163.5 °C (recrystallized in ethyl acetate); IR (KBr) 3300, 3280, 3260, 3080, 1690, 1680, 1650 br, 1580, 1570, 1520, 1490, 1140 cm<sup>-1</sup>; <sup>1</sup>H NMR (300 MHz, DMSO-d<sub>6</sub>) δ 1.96 (s, 3H), 4.27 (dd, J = 15.3, 5.8 Hz, 1H), 4.36 (dd, J = 15.3, 6.2 Hz, 1H), 6.27 (dt, J = 6.8, 1.1 Hz, 1H), 6.39 (bd, J = 8.9 Hz, 1H), 6.71 (d, J = 8.7 Hz, 1H), 7.22-7.34 (m, 5H), 7.43 (ddd, J = 8.9, 6.8, 1.9 Hz, 1H), 7.59 (dd, J = 6.8, 1.9 Hz, 1H), 8.93 (br t, J = 5.9 Hz, 1H), 9.20 (d, J = 8.7 Hz, 1H); <sup>13</sup>C NMR (75 MHz, DMSO-d<sub>6</sub>) 22.4, 42.5, 62.5, 105.1, 119.4, 126.8, 127.1 (2C), 128.2 (2C), 135.6, 138.8, 140.1, 161.1, 166.0, 169.9 ppm; FD (Lilly) mass spectrum, m/e (relative intensity) 598 (2M, 2), 300 (M<sup>+</sup>+1, 17), 299 (M<sup>+</sup>, 100), 96 (2), 95 (26). C<sub>16</sub>H<sub>17</sub>N<sub>3</sub>O<sub>3</sub>.

Anal. Calcd for C, 64.20, H 5.73, N 14.04.

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## EXAMPLE 81

$\alpha$ -acetamido-N-benzyl-2-pyridyl acetamide N-oxide

To a cooled solution of 2- $\alpha$ -acetamido-N-benzyl-2-pyridylacetamide dissolved in dry THF is added m-perchloroperbenzoic acid to give the resulting product.

Similarly, using the procedure described hereinabove, the following examples are prepared.

2-acetamido-N-benzyl-2-(3-pyridyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(4-pyridyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(2-pyrimidinyl)acetamide and the N-oxide thereof

2-acetamido-N-benzyl-2-(4-pyrimidinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(5-pyrimidinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(3-pyridazinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(4-pyridazinyl)acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(4-pyrazinyl) acetamide and the N-oxide thereof,

2-acetamido-N-benzyl-2-(2-thiazolyl)acetamide,

2-acetamido-N-benzyl-2-(2-oxazolyl)acetamide,

2-acetamido-N-benzyl-2-(3-isoxazolyl)acetamide,

2-acetamido-N-benzyl-2-(5-isoxatolyl)acetamide,

2-acetamido-N-benzyl-2-(3-isothiazolyl)acetamide, and

2-acetamido-N-benzyl-2-(5-isothiazolyl)acetamide.

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General Procedure. 2-Acetamido-N-benzyl-2-ethoxyacetamide (1equiv.) was suspended in anhydrous ethyl ether, and then boron trifluoride etherate (1.6-6.3 equiv.) was rapidly added and the resulting solution was stirred for 15 min. The aromatic substrate (1.6-16 equiv.) was then added and the reaction was stirred at room temperature (1-7 days).

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EXAMPLE 82

1  $\alpha$ -Acetamido-N-benzyl-2-(S-thiophenoxy)-acetamide  
(II). The reaction mixture was treated with an aqueous  
saturated  $\text{NaHCO}_3$  solution and the white insoluble solid was  
filtered and then washed successively with  $\text{H}_2\text{O}$  and hexanes.  
5 The desired product was purified by recrystallization from  
chloroform hexanes to give II in 94% yield:  $R_f$  0.43 (97:3  
chloroform/methanol): m.p. 165-167°: i.r. (KBr) 3280, 1630  
(br), 1520 (br), 1430, 1365, 1280, 1245, 1180  $\text{cm}^{-1}$ ;  $^1\text{H}$  n.m.r.  
(DMSO- $d_6$ ) 8.1.83 (s,  $\text{CH}_3\text{CO}$ ). 4.22-4.36 (m,  $\text{CH}_2$ ), 5.90 (d, J =  
10 9.0 Hz, NH), 8.84 (t, J = 5.4 Hz, NH);  $^{13}\text{C}$  n.m.r. (DMSO- $d_6$ )  
22.34 ( $\text{CH}_3\text{CO}$ ), 42.25 ( $\text{CH}_2$ ), 57.65 (CH). 126.86 ( $\text{C}_4'$ ), 127.20  
( $2\text{C}_2'$ ), 123.73 ( $\text{C}_4'$ ). 128.28 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ), 128.88 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ),  
132.36 ( $2\text{C}_3'$ ), 132.51 ( $\text{C}_1'$ ), 138.76 ( $\text{C}_1'$ ), 167.09 (CONH), 168.97  
( $\text{CH}_3\text{CO}$ ) ppm; mass spectrum, m/e (relative intensity) 315 (M +  
15 1,1), 205 (17), 163 (40), 138 (8), 110 (90), 109 (29), 106  
(96), 93 (35), 91 (100).

20 Anal. calc. for  $\text{C}_{17}\text{H}_{18}\text{N}_2\text{O}_2\text{S}$ : C 64.94, H 5.77. Found: C 65.27, H  
5.54.

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Example 83

1        **Synthesis of  $\alpha$ -Acetamido-N-benzyl-2-(tetrahydrofuran)acetamide (3).** A  
methanolic solution (70 mL) of  $\alpha$ -acetamido-N-benzyl-2-furanacetamide (3.50 g,  
12.85 mmol) was hydrogenated (35-40 psi) in the presence of Pd/C (10%, 0.44 g) (44  
5 h). The catalyst was filtered through celite, washed with MeOH (10 mL) and the  
filtrate concentrated to dryness *in vacuo* to give 3a and 3b (3.50 g) as a white solid.  
The products were fractionally recrystallized from EtOAc to give 1.30 g (37%) of 3a:  
mp 159-161 °C;  $R_f$  0.38 (6% MeOH/CHCl<sub>3</sub>); IR (KBr) 3340 (br), 3000, 1600, 1550 (br),  
10 1420, 1350, 720, 680 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.66-1.90 (m, C<sub>3</sub>H<sub>2</sub>, C<sub>4</sub>H<sub>2</sub>), 1.85  
(C(O)CH<sub>3</sub>), 3.62-3.68 (m, C<sub>5</sub>HH'), 3.75-3.80 (m, C<sub>5</sub>HH'), 3.98-4.00 (m, C<sub>2</sub>H), 4.26-4.38  
(m, CH, CH<sub>2</sub>), 7.18-7.32 (m, 5 PhH), 8.11 (d,  $J$  = 8.8 Hz, NH), 8.52 (t,  $J$  = 5.8 Hz,  
15 NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.52 (C(O)CH<sub>3</sub>), 24.78 (C<sub>3</sub>), 27.82 (C<sub>4</sub>), 41.96 (CH<sub>2</sub>), 55.67  
(CH), 67.54 (C<sub>5</sub>), 78.48 (C<sub>2</sub>), 126.58 (C<sub>4</sub>'), 127.97 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.12 (2C<sub>2</sub>' or 2C<sub>3</sub>'),  
139.27 (C<sub>1</sub>'), 169.09 (C(O)NH), 170.09 (C(O)CH<sub>3</sub>) ppm; mass spectrum  $m/e$  (relative  
20 intensity) 277 (M<sup>++1</sup>, 4), 206 (52), 142 (13), 106 (38), 91 (100), 71 (97). Anal.  
(C<sub>15</sub>H<sub>20</sub>N<sub>2</sub>O<sub>3</sub>) C, H, N.

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1        The remaining EtOAc mother liquor after recrystallization was  
concentrated to half its volume and hexane was added dropwise while heating  
until the solution became turbid. A white solid (0.65 g, 18%) separated on cooling  
5 and was collected by filtration to give diastereoisomer 3b: mp 130-132 °C;  $R_f$  0.38  
(6% MeOH/ $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.55-1.86 (m,  $\text{C}_3\text{H}_2$ ,  $\text{C}_4\text{H}_2$ ), 1.89 (s,  
 $\text{C}(\text{O})\text{CH}_3$ ), 3.55-3.64 (m,  $\text{C}_5\text{HH}'$ ), 3.70-3.78 (m,  $\text{C}_5\text{HH}'$ ), 4.08-4.11 (m,  $\text{C}_2\text{H}$ ), 4.27 (d,  $J$   
 $= 5.8$  Hz,  $\text{CH}_2$ ), 4.36 (dd,  $J = 4.7, 8.6$  Hz,  $\text{CH}$ ), 7.21-7.32 (m, 5  $\text{PhH}$ ), 7.94 (d,  $J = 8.6$   
10 Hz,  $\text{NH}$ ), 8.39 (t,  $J = 5.8$  Hz,  $\text{NH}$ );  $^{13}\text{C}$  NMR ( $\text{DMSO}-d_6$ ) 22.45 ( $\text{C}(\text{O})\text{CH}_3$ ), 25.16 ( $\text{C}_4$ ),  
27.53 ( $\text{C}_3$ ), 42.04 ( $\text{CH}_2$ ), 55.48 ( $\text{CH}$ ), 67.53 ( $\text{C}_5$ ), 78.26 ( $\text{C}_2$ ), 126.59 ( $\text{C}_4'$ ), 127.04 ( $2\text{C}_2'$  or  
 $2\text{C}_3'$ ), 128.10 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ), 139.21 ( $\text{C}_1'$ ), 169.55 ( $\text{C}(\text{O})\text{NH}$ ), 169.79 ( $\text{C}(\text{O})\text{CH}_3$ ) ppm;  
15 mass spectrum  $m/e$  (relative intensity) 277 ( $\text{M}^++1$ , 4), 206 (50), 142 (23), 106 (39), 91  
(100), 71 (96). Anal. ( $\text{C}_{15}\text{H}_{20}\text{N}_2\text{O}_3$ ) C, H, N.

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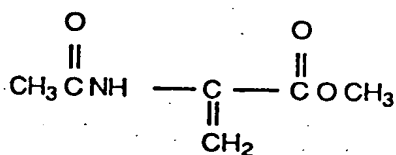
Example 84

1 *Synthesis of Methyl  $\alpha$ -Acetamido-2-methyl-2-furanacetate (17).* HBr was  
 bubbled (2.5 min) through a  $\text{CDCl}_3$  solution (25 mL) of 15 (3.80 g, 26.6 mmol). The  
 excess HBr and  $\text{CDCl}_3$  were removed by evaporating the solution with a  
 5 continuous stream of Ar (20-30 min). The light yellow oily residue that remained  
 containing 16 was dissolved in THF (100 mL), and then furan (32.76 g, 482.0  
 mmol) and  $\text{ZnCl}_2$  (1 M in ether, 53.0 mL, 53.0 mmol) were added. The reaction  
 was stirred at room temperature (3.5 h) and then treated with  $\text{H}_2\text{O}$  (50 mL). The  
 10 aqueous mixture was extracted with EtOAc ( $3 \times 100$  mL), and the combined  
 extracts were dried ( $\text{Na}_2\text{SO}_4$ ). The volatile materials were removed by distillation  
 in vacuo to give 5.00 g (89%) of 17:  $R_f$  0.35 (50%, EtOAc/ $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$   
 1.94 (s,  $\text{CH}_3$ ), 1.99 (s,  $\text{C(O)CH}_3$ ), 3.74 (s,  $\text{C(O)OCH}_3$ ), 6.36 (br s,  $\text{C}_3\text{H}$ ,  $\text{C}_4\text{H}$ ), 6.83 (s,  
 15 NH), 7.35 (s,  $\text{C}_5\text{H}$ );  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 21.43 ( $\text{CH}_3$ ), 23.26 ( $\text{C(O)CH}_3$ ), 53.03  
 ( $\text{C(O)OCH}_3$ ), 58.36 ( $\text{C(CH}_3\text{)}$ ), 107.39 ( $\text{C}_4$ ), 110.52 ( $\text{C}_3$ ), 142.10 ( $\text{C}_5$ ), 152.03 ( $\text{C}_2$ ), 169.21  
 ( $\text{C(O)CH}_3$ ), 171.34 ( $\text{C(O)OCH}_3$ ) ppm.

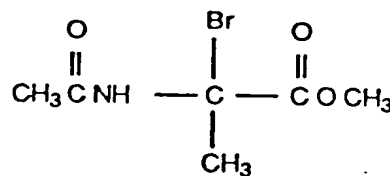
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Example 85

1        *Synthesis of  $\alpha$ -Acetamido-2-methyl-2-furanacetic Acid (18).* A 95% EtOH  
solution (150 mL) of 17 (5.00 g, 23.6 mmol) and KOH (3.00 g, 53.5 mmol) was stirred  
at room temperature (48 h). The solvent was removed and the residue was  
5 dissolved in H<sub>2</sub>O (50 mL). The aqueous solution was washed with Et<sub>2</sub>O (3  $\times$  50 mL)  
and then acidified to pH 1.5 with 10% H<sub>3</sub>PO<sub>4</sub>. The acidified solution was extracted  
with EtOAc (3  $\times$  200 mL) and the combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and  
concentrated *in vacuo* to give 2.90 g (62%) of 18: mp 178-180 °C (d) (recrystallized  
10 from CH<sub>3</sub>CN); IR (KBr) 3400 (br), 1700 (br) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.67 (s,  
CH<sub>3</sub>), 1.83 (s, C(O)CH<sub>3</sub>), 6.39 (m, C<sub>3</sub>H, C<sub>4</sub>H), 7.59 (s, C<sub>5</sub>H), 8.34 (s, NH), 12.63 (s,  
C(O)OH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.20 (C(O)CH<sub>3</sub>), 22.59 (CH<sub>3</sub>), 57.65 (C(CH<sub>3</sub>)), 107.09  
(C<sub>4</sub>), 110.49 (C<sub>3</sub>), 142.33 (C<sub>5</sub>), 153.36 (C<sub>2</sub>), 168.86 (C(O)NH), 171.78 (C(O)OH) ppm;  
15 mass spectrum, m/e (relative intensity) 198 (M<sup>+</sup>+1, 4), 143 (97), 152 (63), 140 (23),  
111 (73), 110 (100), 94 (24). Anal. (C<sub>9</sub>H<sub>11</sub>NO<sub>4</sub>) C, H, N.

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Example 86

*Synthesis of  $\alpha$ -Acetamido-N-benzyl-2-methyl-2-furanacetamide (4).*

1 Employing the mixed carbonic anhydride coupling procedure<sup>51g</sup> with **18** (2.40 g,  
12.2 mmol), 4-methylmorpholine (1.23 g, 12.2 mmol), isobutylchloroformate (1.83  
g, 13.4 mmol), and benzylamine (1.43 g, 12.7 mmol) gave **4** (1.50 g, 43%) as a thick  
5 oil:  $R_f$  0.29 (2% MeOH/CHCl<sub>3</sub>); <sup>1</sup>H NMR (CDCl<sub>3</sub>)  $\delta$  1.94 (s, CH<sub>3</sub>), 1.98 (s, C(O)CH<sub>3</sub>),  
4.40 (d,  $J$  = 5.6 Hz, CH<sub>2</sub>), 6.20 (br s, NH), 6.34-6.37 (m, C<sub>3</sub>H, C<sub>4</sub>H), 7.05-7.36 (m, NH,  
C<sub>5</sub>H, 5 PhH); <sup>13</sup>C NMR (CDCl<sub>3</sub>) 22.31 (C(O)CH<sub>3</sub>), 23.81 (CH<sub>3</sub>), 43.77 (CH<sub>2</sub>), 58.50  
10 (C(CH<sub>3</sub>)), 107.94 (C<sub>4</sub>), 110.67 (C<sub>3</sub>), 126.99 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 127.41 (C<sub>4'</sub>), 128.60 (2C<sub>2'</sub> or  
2C<sub>3'</sub>), 137.52 (C<sub>1'</sub>), 142.38 (C<sub>5</sub>), 152.94 (C<sub>2</sub>), 169.03 (C(O)NH), 171.16 (COCH<sub>3</sub>) ppm;  
mass spectrum,  $m/e$  (relative intensity) 287 (M<sup>++1</sup>, 4), 228 (4), 153 (99), 152 (96), 138  
(15), 111 (63), 110 (100), 91 (75);  $M_r$  (EI) 286.13074 (calcd for C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>, 286.13174).

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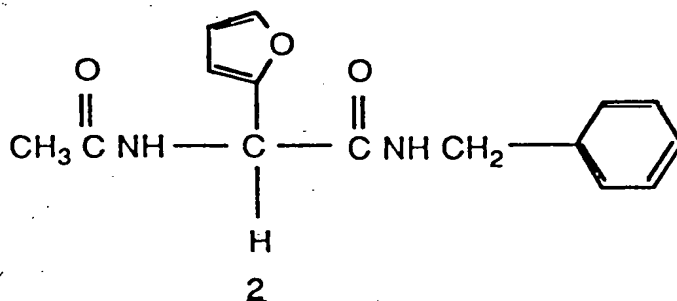
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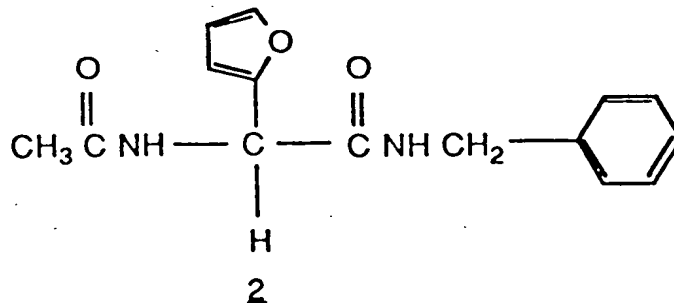
## Example 87

1 **Synthesis of  $\alpha$ -Thioacetamido-N-benzyl-2-furanacetamide (5).** A THF  
 solution (80 mL) of 2 (1.00 g, 3.68 mmol) and Lawesson's reagent (0.73 g, 1.84  
 mmol) was stirred at room temperature (4 h). The THF was removed *in vacuo*  
 5 and the residue was purified by flash column chromatography on SiO<sub>2</sub> gel using  
 1% MeOH/CHCl<sub>3</sub> to give 0.75 g (71%) of 5: mp 78-80 °C; R<sub>f</sub> 0.51 (1% MeOH/CHCl<sub>3</sub>);  
 IR (KBr) 3200 (br), 1630, 1500, 1440, 1350, 790, 710, 680 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$   
 2.46 (s, C(S)CH<sub>3</sub>), 4.27-4.35 (m, CH<sub>2</sub>), 6.22 (d,  $J$  = 7.7 Hz, CH), 6.32 (d,  $J$  = 3.3 Hz,  
 10 C<sub>3</sub>H), 6.41-6.44 (m, C<sub>4</sub>H), 7.15-7.33 (m, 5 PhH), 7.64 (s, C<sub>5</sub>H), 8.81 (t,  $J$  = 5.9 Hz,  
 NH), 10.54 (d,  $J$  = 7.7 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 32.70 (s, C(S)CH<sub>3</sub>), 42.39 (CH<sub>2</sub>),  
 56.82 (CH), 108.76 (C<sub>3</sub>), 110.67 (C<sub>4</sub>), 126.81 (C<sub>4'</sub>), 127.12 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.23 (2C<sub>2'</sub> or  
 2C<sub>3'</sub>), 139.98 (C<sub>1'</sub>), 143.06 (C<sub>5</sub>), 149.53 (C<sub>2</sub>), 166.55 (C(O)NH), 200.68 (C(S)CH<sub>3</sub>) ppm;  
 15 mass spectrum (FD) 288 (M<sup>+</sup>). Anal. (C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>O<sub>2</sub>S) C, H, N.



Example 88

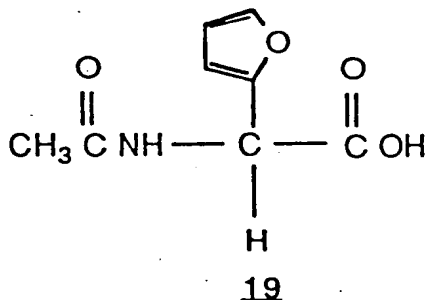
1        **Synthesis of  $\alpha$ -Thioacetamido-N-benzyl-2-furanthioacetamide (6).** A THF  
 solution (90 mL) of **2** (2.00 g, 7.35 mmol) and Lawesson's reagent (3.27 g, 8.09  
 mmol) was heated to reflux (4 h). The THF was removed *in vacuo* and the residue  
 5 was purified by two successive flash column chromatographies on SiO<sub>2</sub> gel using  
 0.5% MeOH/CHCl<sub>3</sub> as the eluant in the first chromatography and CHCl<sub>3</sub> in the  
 second chromatography. Compound **6** (0.50 g, 22%) was then further purified by  
 preparative TLC (CHCl<sub>3</sub>): mp 99-101 °C; R<sub>f</sub> 0.74 (1% MeOH/CHCl<sub>3</sub>); IR (KBr) 3100,  
 10 1580, 1500 (br) cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  2.58 (s, C(S)CH<sub>3</sub>), 4.86 (dd, *J* = 5.4, 15.0  
 Hz, CHH), 4.96 (dd, *J* = 5.4, 15.0 Hz, CHH), 6.49-6.55 (m, C<sub>3</sub>H, C<sub>4</sub>H), 6.65 (d, *J* = 7.5  
 Hz, CH), 7.31-7.43 (m, 5 PhH), 7.75 (s, C<sub>5</sub>H) 10.64 (d, *J* = 7.5 Hz, NH), 10.95 (t, *J* =  
 5.4 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 32.79 (s, C(S)CH<sub>3</sub>), 48.30 (CH<sub>2</sub>), 61.88 (CH),  
 15 108.50 (C<sub>3</sub>), 110.53 (C<sub>4</sub>), 127.05 (C<sub>4'</sub>), 127.48 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.19 (2C<sub>2'</sub> or 2C<sub>3'</sub>),  
 136.67 (C<sub>1'</sub>), 142.91 (C<sub>5</sub>), 150.15 (C<sub>2</sub>), 197.45 (C(S)NH), 200.56 (C(S)CH<sub>3</sub>) ppm; mass  
 spectrum (FD) 304 (M<sup>+</sup>). Anal. (C<sub>15</sub>H<sub>16</sub>N<sub>2</sub>OS<sub>2</sub>) C, H, N.



Example 89

1 **Synthesis of  $\alpha$ -Acetamido-N-(3-pyridinylmethyl)-2-furanacetamide (7).**

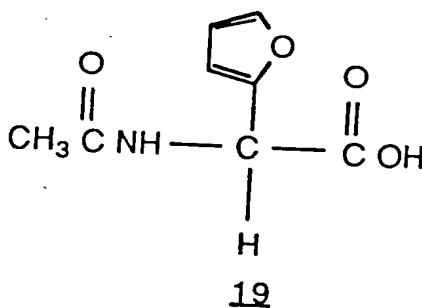
Using racemic 19 (3.00 g, 16.39 mmol), 4-methylmorpholine (1.66 g, 16.39 mmol),  
isobutylchloroformate (2.24 g, 16.39 mmol), and 3-aminomethylpyridine (1.77 g,  
5 16.39 mmol) in the mixed carbonic anhydride protocol gave 3.35 g (75%) of 7: mp  
172-174 °C (recrystallized from EtOAc);  $R_f$  0.27 (8% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400,  
3300, 1640, 1540, 1420, 1360, 820, 740 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.89 (s, C(O)CH<sub>3</sub>),  
4.32 (d,  $J$  = 5.8 Hz, CH<sub>2</sub>), 5.55 (d,  $J$  = 7.9 Hz, CH), 6.28-6.29 (m, C<sub>3</sub>H), 6.41-6.43 (m,  
10 C<sub>4</sub>H), 7.32 (dd,  $J$  = 4.8, 7.7 Hz, C<sub>5</sub>H), 7.58-7.62 (m, C<sub>4</sub>H, C<sub>5</sub>H), 8.44 (br s, C<sub>2</sub>H,  
C<sub>6</sub>H), 8.62 (d,  $J$  = 7.9 Hz, NH), 8.81 (t,  $J$  = 5.8 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.31  
(C(O)CH<sub>3</sub>), 39.98 (CH<sub>2</sub>), 50.94 (CH), 107.67 (C<sub>4</sub>), 110.54 (C<sub>3</sub>), 123.38 (C<sub>5</sub>'), 134.57  
(C<sub>3</sub>'), 134.83 (C<sub>4</sub>'), 142.64 (C<sub>5</sub>), 148.06 (C<sub>6</sub>'), 148.55 (C<sub>2</sub>'), 150.94 (C<sub>2</sub>), 168.19  
15 (C(O)NH), 169.26 (C(O)CH<sub>3</sub>) ppm; mass spectrum (FD) 274 (M<sup>++1</sup>). Anal.  
(C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>) C, H, N.



Example 90

1 *Synthesis of  $\alpha$ -Acetamido-N-(4-pyridinylmethyl)-2-furanacetamide (8).*

Making use of racemic 19 (3.00 g, 16.39 mmol), 4-methylmorpholine (1.66 g, 16.39 mmol), isobutylchloroformate (2.24 g, 16.39 mmol), and 4-aminomethylpyridine  
 5 (1.77 g, 16.39 mmol) in the mixed carbonic anhydride method, gave 3.40 g (76%) of 8: mp 168-170 °C (recrystallized from EtOAc);  $R_f$  0.31 (8% MeOH/CHCl<sub>3</sub>); IR (KBr) 3180, 1650 (br), 1480, 1400, 1340, 780, 740 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.90 (s, C(O)CH<sub>3</sub>), 4.32 (d,  $J$  = 5.7 Hz, CH<sub>2</sub>), 5.57 (d,  $J$  = 7.8 Hz, CH), 6.32-6.34 (m, C<sub>3</sub>H),  
 10 6.42-6.43 (m, C<sub>4</sub>H), 7.19 (d,  $J$  = 4.9 Hz, C<sub>3'</sub>H, C<sub>5'</sub>H), 7.64 (s, C<sub>5</sub>H), 8.46 (d,  $J$  = 4.9 Hz, C<sub>2'</sub>H, C<sub>6'</sub>H), 8.64 (d,  $J$  = 7.8 Hz, NH), 8.84 (t,  $J$  = 5.7 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.27 (C(O)CH<sub>3</sub>), 41.26 (CH<sub>2</sub>), 50.99 (CH), 107.74 (C<sub>4</sub>), 110.54 (C<sub>3</sub>), 121.87 (C<sub>3'</sub>, C<sub>5'</sub>),  
 15 142.63 (C<sub>5</sub>), 148.17 (C<sub>4'</sub>), 149.35 (C<sub>2'</sub>, C<sub>6'</sub>), 150.82 (C<sub>2</sub>), 168.35 (C(O)NH), 169.29 (C(O)CH<sub>3</sub>) ppm; mass spectrum (FD) 274 (M<sup>+</sup>+1). Anal. (C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>3</sub>) C, H, N.



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Example 91*Synthesis of  $\alpha$ -Acetamido-N-(1-oxo-3-pyridinylmethyl)-2-furanacetamide*

1 (9). A solution of 7 (1.50 g, 5.49 mmol) and m-chloroperoxybenzoic acid (1.90 g,  
6.04 mmol) in THF (175 mL) was heated to reflux (3 h) and then cooled to room  
5 temperature. The THF solution was concentrated to approximately half its  
volume, and then cooled to give 1.00 g (63%) of 9: mp 159-161 °C (recrystallized  
from EtOH);  $R_f$  0.30 (20% MeOH/ $\text{CHCl}_3$ ); IR (KBr) 3400 (br), 1620, 1500 (br), 1420,  
1350, 750  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  1.89 (s,  $\text{C(O)CH}_3$ ), 4.27 (d,  $J = 5.0$  Hz,  $\text{CH}_2$ ),  
10 5.53 (d,  $J = 7.6$  Hz, CH), 6.31 (br s,  $\text{C}_3\text{H}$ ), 6.42 (br s,  $\text{C}_4\text{H}$ ), 7.14-7.18 (m, 1 ArH), 7.31-  
7.37 (m, 1 ArH), 7.61 (br s,  $\text{C}_5\text{H}$ ), 8.07 (s, 2 ArH), 8.63 (br s, NH), 8.80 (br s, NH);  
 $^{13}\text{C}$  NMR ( $\text{DMSO-d}_6$ ) 22.29 ( $\text{C(O)CH}_3$ ), 39.36 ( $\text{CH}_2$ ), 50.99 (CH), 107.79 ( $\text{C}_4$ ), 110.56  
( $\text{C}_3$ ), 124.03 ( $\text{C}_4'$ ), 126.10 ( $\text{C}_5'$ ), 137.16 ( $\text{C}_3'$ ), 137.31 ( $\text{C}_6'$ ), 138.70 ( $\text{C}_2'$ ), 142.69 ( $\text{C}_5$ ),  
15 150.72 ( $\text{C}_2$ ), 168.40 ( $\text{C(O)NH}$ ), 169.32 ( $\text{C(O)CH}_3$ ) ppm; mass spectrum (FD) 289 ( $\text{M}^+$ );  
 $M_r$  (EI) 289.10554 (calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_4$ , 289.10626).

Anal. Calcd for  $\text{C}_{14}\text{H}_{15}\text{N}_3\text{O}_4 \cdot 2.0 \text{ H}_2\text{O}$ : C, 51.69; H, 5.89; N, 12.92. Found: C,  
52.03; H, 5.56; N, 13.36.

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Example 92

1        *Synthesis of  $\alpha$ -Acetamido-N-(1-oxo-4-pyridinylmethyl)-2-furanacetamide*  
2        (10). Following the preceding procedure and using 8 (1.50 g, 5.49 mmol) and m-  
3        chloroperoxybenzoic acid (1.90 g, 6.04 mmol) gave a light yellow solid (0.96 g, 60%)  
4        directly upon cooling the THF solution. The precipitate was filtered and  
5        recrystallized from EtOH to give 10: mp 210-212 °C (d);  $R_f$  0.25 (20% MeOH/CHCl<sub>3</sub>);  
6        IR (KBr) 3300, 1620, 1500, 1410, 1350, 740 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.89 (s,  
7        C(O)CH<sub>3</sub>), 4.26 (d,  $J$  = 5.8 Hz, CH<sub>2</sub>), 5.52 (d,  $J$  = 7.7 Hz, CH), 6.30 (br s, C<sub>3</sub>H), 6.41-  
8        6.42 (m, C<sub>4</sub>H), 7.21 (d,  $J$  = 6.8 Hz, C<sub>3'</sub>H, C<sub>5'</sub>H), 7.63 (s, C<sub>5</sub>H), 8.14 (d,  $J$  = 6.8 Hz,  
9        C<sub>2'</sub>H, C<sub>6'</sub>H), 8.62 (d,  $J$  = 7.7 Hz, NH), 8.82 (t,  $J$  = 5.8 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  
10        22.35 (C(O)CH<sub>3</sub>), 40.68 (CH<sub>2</sub>), 51.14 (CH), 107.87 (C<sub>4</sub>), 110.62 (C<sub>3</sub>), 124.83 (C<sub>3'</sub>, C<sub>5'</sub>),  
11        137.43 (C<sub>4'</sub>), 138.39 (C<sub>2'</sub>, C<sub>6'</sub>), 142.72 (C<sub>5</sub>), 150.77 (C<sub>2</sub>), 168.48 (C(O)NH), 169.45  
12        (C(O)CH<sub>3</sub>) ppm; mass spectrum (FD) 289 (M<sup>+</sup>). Anal. (C<sub>14</sub>H<sub>15</sub>N<sub>3</sub>O<sub>4</sub>) C, H, N.

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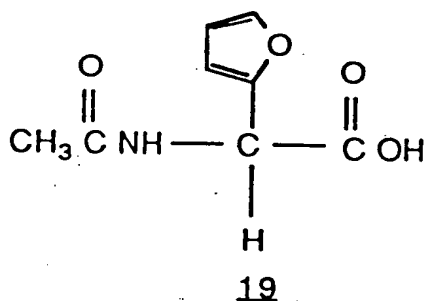
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Example 93

1 *Synthesis of  $\alpha$ -Acetamido-2-furanacetic-2'-pyridinehydrazide (11).*

Following the mixed carbonic anhydride procedure and using racemic 19 (2.00 g, 10.39 mmol), 4-methylmorpholine (1.10 g, 10.93 mmol), isobutylchloroformate (1.49 g, 10.93 mmol), and 2-hydrazinopyridine (1.20 g, 11.00 mmol) gave an insoluble material upon workup containing 11 and 4-methylmorpholine hydrochloride. The reaction products were suspended in EtOH (25 mL), and 11 (1.00 g) was collected by filtration. Concentration of the THF filtrate and trituration of the residue with EtOAc gave an additional 0.70 g of 11 to give a combined yield of 1.70 g (64%): mp 226-228 °C (recrystallized from EtOH);  $R_f$  0.30 (10% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400, 1650, 1580, 1440, 1360, 1320, 770, 730 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.83 (s, C(O)CH<sub>3</sub>), 5.64 (d,  $J$  = 8.0 Hz, CH), 6.41-6.50 (m, C<sub>3</sub>H, C<sub>4</sub>H, C<sub>5</sub>H), 6.67 (dd,  $J$  = 5.4, 6.7 Hz, C<sub>3</sub>H), 7.44-7.52 (m, C<sub>4</sub>H), 7.66 (s, C<sub>5</sub>H), 8.02 (d,  $J$  = 4.0 Hz, C<sub>6</sub>H), 8.40 (s, C(O)NHNH), 8.66 (d,  $J$  = 8.0 Hz, NH), 10.20 (s, C(O)NHNH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.26 (C(O)CH<sub>3</sub>), 49.56 (CH), 105.93 (C<sub>3</sub>'), 107.87 (C<sub>3</sub>), 110.57 (C<sub>4</sub>), 114.50 (C<sub>5</sub>'), 137.48 (C<sub>4</sub>'), 142.76 (C<sub>5</sub>), 147.45 (C<sub>6</sub>'), 150.60 (C<sub>2</sub>), 159.59 (C<sub>2</sub>'), 167.88 (C(O)NH), 169.28 (C(O)CH<sub>3</sub>) ppm; mass spectrum (FD) 274 (M<sup>+</sup>);  $M_r$  (EI) 274.10649 (calcd for C<sub>13</sub>H<sub>14</sub>N<sub>4</sub>O<sub>3</sub>, 274.10659).



Example 94

1      *Synthesis of R(-)α-Acetamido-N-(4-fluorobenzyl)-2-furanacetamide ((R)-12).*

Using (R)-19 (0.94 g, 5.1 mmol), 4-methylmorpholine (0.52 g, 5.1 mmol),  
isobutylchloroformate (0.70 g, 5.1 mmol), and 4-fluorobenzylamine (0.65 g, 5.16  
5 mmol) in the mixed carbonic anhydride method gave 1.00 g (68%) of (R)-12: mp  
205-207 °C (recrystallized from EtOAc);  $R_f$  0.30 (4% MeOH/CHCl<sub>3</sub>);  $[\alpha]^{26}_D = -77.42$   
(c=1, MeOH); IR (KBr) 3400 (br), 1620, 1580, 1500 (br), 1350, 770, 720 cm<sup>-1</sup>; <sup>1</sup>H NMR  
(DMSO-d<sub>6</sub>) δ 1.89 (s, C(O)CH<sub>3</sub>), 4.27 (d,  $J = 5.9$  Hz, CH<sub>2</sub>), 5.54 (d,  $J = 8.0$  Hz, CH),  
10 6.27 (d,  $J = 3.0$  Hz, C<sub>3</sub>H), 6.41 (dd,  $J = 1.9, 3.0$  Hz, C<sub>4</sub>H), 7.08-7.15 (m, 2 ArH), 7.20-  
7.26 (m, 2 ArH), 7.61 (d,  $J = 1.9$  Hz, C<sub>5</sub>H), 8.58 (d,  $J = 8.0$  Hz, NH), 8.74 (t,  $J = 5.9$   
Hz, NH) ppm; addition of R(-) mandelic acid to a CDCl<sub>3</sub> solution of (R)-12 gave only  
15 one signal for the acetamide methyl protons. Mass spectrum (FD) 290 (M<sup>+</sup>).  
Anal. (C<sub>15</sub>H<sub>15</sub>FN<sub>2</sub>O<sub>3</sub>) C, H, N.

*Synthesis of R(-)α-Acetamido-N-(4-methylbenzyl)-2-furanacetamide ((R)-13).*

Employing the mixed carbonic anhydride procedure and making use of (R)-19  
20 (1.50 g, 8.20 mmol), 4-methylmorpholine (0.83 g, 8.20 mmol), isobutylchloroformate  
(1.12 g, 8.20 mmol), and 4-methylbenzylamine (0.99 g, 8.20 mmol) gave 1.80 g  
(77%) of (R)-13: mp 210-212 °C (recrystallized from EtOAc);  $R_f$  0.54 (4%  
MeOH/CHCl<sub>3</sub>);  $[\alpha]^{26}_D = -74.43$  (c=1, MeOH); IR (KBr) 3400 (br), 1610 (br), 1500 (br),  
25 1350, 1320, 780, 720 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.89 (s, C(O)CH<sub>3</sub>), 2.25 (s, CH<sub>3</sub>),  
4.24 (d,  $J = 5.5$  Hz, CH<sub>2</sub>), 5.56 (d,  $J = 8.1$  Hz, CH), 6.28 (br s, C<sub>3</sub>H), 6.41 (br s, C<sub>4</sub>H),  
7.09 (br s, 4ArH), 7.61 (br s, C<sub>5</sub>H), 8.58 (d,  $J = 8.1$  Hz, NH), 8.72 (t,  $J = 5.5$  Hz, NH);  
addition of (R)-mandelic acid to a CDCl<sub>3</sub> solution of (R)-13 gave only one signal  
30 for the acetamide methyl protons. <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 20.64 (CH<sub>3</sub>), 22.32  
(C(O)CH<sub>3</sub>), 42.00 (CH<sub>2</sub>), 50.88 (CH), 107.52 (C<sub>4</sub>), 110.50 (C<sub>3</sub>), 127.06 (2C<sub>2'</sub> or 2C<sub>3'</sub>),  
128.77 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 135.82 (C<sub>1'</sub> or C<sub>4'</sub>), 135.98 (C<sub>1'</sub> or C<sub>4'</sub>), 142.51 (C<sub>5</sub>), 151.21 (C<sub>2</sub>),  
167.87 (C(O)NH), 169.17 (C(O)CH<sub>3</sub>) ppm; mass spectrum (FD) 287 (M<sup>+</sup>+1). Anal.  
35 (C<sub>16</sub>H<sub>18</sub>N<sub>2</sub>O<sub>3</sub>) C, H, N.

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Example 95

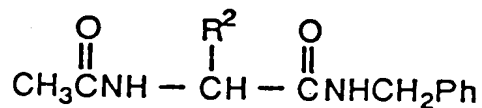
1        *Synthesis of R(-)- $\alpha$ -Acetamido-N-(4-trifluoromethylbenzyl)-2-furanaceta-*  
       *midate ((R)-14).* Using (R)-19 (1.00 g, 5.46 mmol), 4-methylmorpholine (0.55 g, 5.46  
       mmol), isobutylchloroformate (0.75 g, 5.46 mmol), and 4-trifluoromethylbenzyl-  
 5 amine (0.96 g, 5.46 mmol) in the mixed carbonic anhydride protocol gave 1.15 g  
       (59%) of (R)-14: mp 193-195 °C (recrystallized from EtOAc/hexane);  $[\alpha]^{26}_D = -69.27$   
       (c=1, MeOH); IR (KBr) 3220, 1610, 1520, 1400, 1350, 800, 720  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (DMSO-  
       d<sub>6</sub>)  $\delta$  1.89 (s, C(O)CH<sub>3</sub>), 4.37 (d,  $J = 5.8$  Hz, CH<sub>2</sub>), 5.56 (d,  $J = 7.9$  Hz, CH), 6.30-6.31  
 10 (m, C<sub>3</sub>H), 6.41-6.43 (m, C<sub>4</sub>H), 7.40-7.43 (m, 2ArH), 7.63-7.68 (m, 2ArH, C<sub>5</sub>H), 8.61  
       (d,  $J = 7.9$  Hz, NH), 8.44 (t,  $J = 5.8$  Hz, NH); addition of (R)(-)-mandelic acid to a  
       CDCl<sub>3</sub> solution of (R)-14 gave only one signal for the acetamide methyl protons.  
       Mass spectrum (FD) 340 (M<sup>+</sup>). Anal. (C<sub>16</sub>H<sub>15</sub>F<sub>3</sub>N<sub>2</sub>O<sub>3</sub>) C, H, N.

GENERAL SYNTHESIS

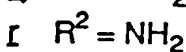
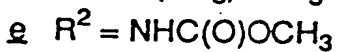
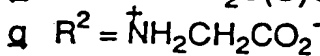
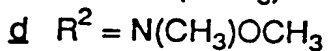
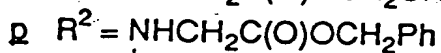
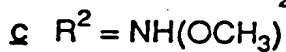
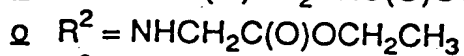
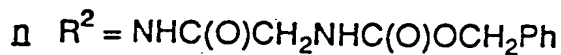
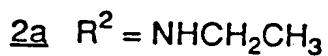
General *Synthesis* - Several preparative routes were utilized for the construction of  
       the targetted compounds. In most cases, 2-acetamido-N-benzyl-2-aminoaceta-  
 20 midate (2r) served as the starting material. Treatment of 2r with the appropriate  
       chloroformate, isocyanate, isothiocyanate, anhydride, or use of the mixed  
       anhydride protocol advanced for peptide synthesis led to the preparation of the N-  
       acyl substituted adducts 2e-2l and 2n. Correspondingly, the preformed  $\alpha$ -bromo  
 25 derivative 2s was employed as the immediate precursor for 2m and 2p, while 2-  
       acetamido-N-benzyl-2-(trimethylammonio)acetamide tetrafluoroborate (2l) was  
       utilized for the synthesis of 2q. Finally, alkaline hydrolysis of 2p, followed by  
 30 neutralization of the dipeptide by passage through an ion exchange resin yielded  
       2q.

In Examples 96-108, reference is made to the  
       following compounds

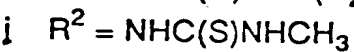
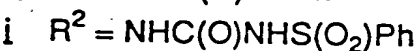
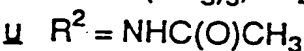
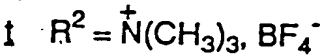
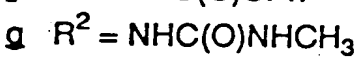
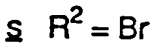
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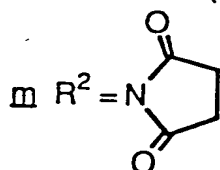
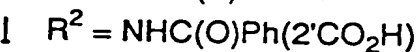
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Example 96

- 1        **Chemistry - Synthesis of Methyl[acetamido(benzylcarbamoyl)methyl]carbamate (2e).** Methyl chloroformate (0.33 g, 3.35 mmol) was added to a solution of 2r  
mate (2e). Methyl chloroformate (0.33 g, 3.35 mmol) was added to a solution of 2r  
(0.70 g, 3.16 mmol) and Et<sub>3</sub>N (0.39 g, 3.80 mmol) in THF (75 mL), and then the  
5 reaction mixture was stirred at 55-60 °C (2 h). The Et<sub>3</sub>N·HCl that precipitated was  
filtered and the filtrate was concentrated to dryness *in vacuo*. The residue was  
trituated with EtOAc (20 mL), and the remaining white solid (0.55 g, 62%) was  
filtered and recrystallized from EtOH: mp 202-204 °C (d); R<sub>f</sub> 0.53 (10%  
10 MeOH/CHCl<sub>3</sub>); IR (KBr) 3260, 1650, 1500, 1440, 1360, 780, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR  
(DMSO-d<sub>6</sub>) δ 1.86 (s, C(O)CH<sub>3</sub>), 3.54 (s, OCH<sub>3</sub>), 4.27 (d, *J* = 5.6 Hz, CH<sub>2</sub>), 5.56 (t, *J* =  
7.8 Hz, CH), 7.18-7.32 (m, 5PhH), 7.70 (br s, NHC(O)OCH<sub>3</sub>), 8.40 (d, *J* = 7.8 Hz,  
15 NH), 8.51 (t, *J* = 5.6 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.38 (C(O)CH<sub>3</sub>), 42.29 (CH<sub>2</sub>),  
51.46 (OCH<sub>3</sub>), 58.57 (CH), 126.52 (C<sub>4'</sub>), 126.98 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 127.99 (2C<sub>2'</sub> or 2C<sub>3'</sub>),  
139.03 (C<sub>1'</sub>), 167.83 (C(O)NH), 169.33 (C(O)CH<sub>3</sub>) ppm, the carbamate carbonyl  
signal was not detected. Mass spectrum (FD) 279 (M<sup>+</sup>).  
20        Anal. Calcd for C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>: C, 55.91; H, 6.14; N, 15.05. Found: C, 56.16;  
H, 6.10; N, 14.89.

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Example 97

*Synthesis of Phenyl[acetamido(benzylcarbamoyl)methyl]carbamate (2f).*

Compound 2r (0.80 g, 3.62 mmol) was dissolved in warm THF (75 mL), and then Et<sub>3</sub>N (0.44 g, 4.35 mmol), and phenyl chloroformate (0.62 g, 3.98 mmol) were added. The reaction mixture was stirred at 45-50 °C (2 h), and the volatile materials were removed *in vacuo*. The residue was triturated with EtOAc (20 mL) and the remaining white solid material (0.80 g, 65%) was filtered, washed with H<sub>2</sub>O (10 mL), and then recrystallized from MeOH: mp 201-203 °C; R<sub>f</sub> 0.38 (5% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400 (br), 3240, 1700, 1630, 1500, 1460, 1320, 1200, 740, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.89 (s, C(O)CH<sub>3</sub>), 4.29-4.35 (m, CH<sub>2</sub>), 5.66 (t, *J* = 7.6 Hz, CH), 7.08-7.42 (m, 10ArH), 8.43 (d, *J* = 7.6 Hz, NH), 8.58 (d, *J* = 7.6 Hz, NH), 8.67 (t, *J* = 5.0 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.58 (C(O)CH<sub>3</sub>), 42.51 (CH<sub>2</sub>), 58.69 (CH), 121.70 (2C<sub>2</sub>), 125.18 (C<sub>4</sub>), 126.76 (C<sub>4'</sub>), 127.19 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.21 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 129.30 (2C<sub>3</sub>), 139.14 (C<sub>1'</sub>), 150.91 (C<sub>1</sub>), 167.73 (C(O)NH), 169.75 (C(O)CH<sub>3</sub>) ppm, the signal for the carbamate carbonyl was not detected. Mass spectrum (FD) 341 (M<sup>+</sup>).

Anal. Calcd for C<sub>18</sub>H<sub>19</sub>N<sub>3</sub>O<sub>4</sub>: C, 63.33; H, 5.61; N, 12.31. Found: C, 63.06; H, 5.64; N, 12.12.

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Example 98

1 *Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-methylurea (2g).*

Methyl isocyanate (0.20 g, 3.48 mmol) was added to a solution of 2r (0.70 g, 3.16 mmol) in THF (75 mL), and then the reaction was stirred at 45-50 °C (2 h). The  
 5 white solid (0.80 g, 91%) that separated out was filtered and recrystallized from MeOH to give 2g: mp 229-230 °C (d);  $R_f$  0.25 (10% MeOH/ $CHCl_3$ ); IR (KBr) 3200, 3060, 1630, 1500 (br), 1350, 1300, 740, 680  $cm^{-1}$ ;  $^1H$  NMR (DMSO- $d_6$ )  $\delta$  1.82 (s,  $C(O)CH_3$ ), 2.54 (d,  $J = 4.5$  Hz,  $NHCH_3$ ), 4.26 (d,  $J = 5.8$  Hz,  $CH_2$ ), 5.59 (t,  $J = 7.8$  Hz, CH), 6.19 (d,  $J = 4.5$  Hz,  $NHCH_3$ ), 6.52 (d,  $J = 7.8$  Hz,  $NHC(O)NHCH_3$ ), 7.20-7.31 (m, 5PhH), 8.38 (t,  $J = 5.8$  Hz, NH), 8.46 (d,  $J = 7.8$  Hz, NH);  $^{13}C$  NMR (DMSO- $d_6$ ) 22.36 ( $C(O)CH_3$ ), 26.03 ( $NHCH_3$ ), 42.19 ( $CH_2$ ), 57.92 (CH), 126.54 ( $C_4'$ ), 126.93 ( $2C_2'$  or  $2C_3'$ ), 128.06 ( $2C_2'$  or  $2C_3'$ ), 139.16 ( $C_1'$ ), 157.30 ( $NHC(O)NH$ ), 168.89 ( $C(O)NH$ ),  
 10 169.37 ( $C(O)CH_3$ ) ppm; mass spectrum (FD) 279 ( $M^{+}+1$ ).  
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Anal. Calcd for  $C_{13}H_{18}N_4O_3$ : C, 56.10; H, 6.52; N, 20.13. Found: C, 56.31; H, 6.41; N, 20.12.

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Example 99

1      *Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-phenylurea (2h).*

Phenyl isocyanate (0.42 g, 3.5 mmol) was added to a solution of 2r (0.70 g, 3.16 mmol) in THF (75 mL), and then the reaction was stirred at 45-50 °C (2 h). The  
5      white solid (0.95 g, 89%) that precipitated.      was filtered and dried: mp 242-244 °C (d);  $R_f$  0.30 (5% MeOH/CHCl<sub>3</sub>); IR (KBr) 3200 (br), 1600 (br), 1430 (br), 1300, 880, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.86 (s, C(O)CH<sub>3</sub>), 4.30 (d,  $J$  = 5.9 Hz, CH<sub>2</sub>), 5.67 (t,  $J$  = 7.6 Hz, CH), 6.86-6.93 (m, 2ArH), 7.20-7.32 (m, NH, 5PhH, 1ArH), 7.37-7.40 (m, 2ArH),  
10      8.56 (t,  $J$  = 5.9 Hz, NH), 8.68 (d,  $J$  = 7.6 Hz, NH), 8.89 (s, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.38 (C(O)CH<sub>3</sub>), 42.29 (CH<sub>2</sub>), 57.59 (CH), 117.61 (2C<sub>2</sub>), 121.37 (C<sub>4</sub>), 126.57 (C<sub>4</sub>'), 126.95 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.07 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.62 (2C<sub>3</sub>), 139.12 (C<sub>1</sub> or C<sub>1</sub>'),  
15      139.98 (C<sub>1</sub> or C<sub>1</sub>'), 153.98 (NHC(O)NH), 168.55 (C(O)NH), 169.58 (C(O)CH<sub>3</sub>) ppm; mass spectrum (FD) 340 (M<sup>+</sup>).

Anal. Calcd for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>: C, 63.52; H, 5.92; N, 16.46. Found: C, 63.22; H, 5.92; N, 16.20.

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Example 100

1        *Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-benzenesulfonylurea*  
 (2i). Benzenesulfonyl isocyanate (0.64 g, 3.48 mmol) was added to a solution of 2r  
 (0.70 g, 3.16 mmol) in THF (75 mL), and then the reaction was stirred at 50-55 °C  
 5 (22 h). The white solid (0.84 g, 66%) that separated on cooling was filtered and  
 dried: mp 188-191 °C (d);  $R_f$  0.11 (10% MeOH/CHCl<sub>3</sub>); IR (KBr) 3250, 1630 (br), 1500  
 (br), 1460, 1330, 870, 700 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.80 (s, C(O)CH<sub>3</sub>), 4.24 (d,  $J$  =  
 5.7 Hz, CH<sub>2</sub>), 5.47 (t,  $J$  = 7.7 Hz, CH), 7.18-7.30 (m, 5PhH, NH), 7.57-7.71 (m, 3ArH),  
 10 7.89-7.92 (d,  $J$  = 7.5 Hz, 2ArH), 8.54 (t,  $J$  = 5.7 Hz, NH), 8.70 (d,  $J$  = 7.7 Hz, NH),  
 10.80 (s, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.29 (C(O)CH<sub>3</sub>), 42.30 (CH<sub>2</sub>), 57.14 (CH), 126.58  
 (C<sub>4'</sub>), 126.89 (2C<sub>2</sub>), 127.12 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.05 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.96 (2C<sub>3</sub>), 133.25  
 (C<sub>4</sub>), 138.88 (C<sub>1</sub> or C<sub>1'</sub>), 139.87 (C<sub>1</sub> or C<sub>1'</sub>), 150.36 (NHC(O)NH), 167.55 (C(O)NH),  
 15 169.55 (C(O)CH<sub>3</sub>) ppm; mass spectrum (FD) 405 (M<sup>+</sup>+1).

Anal. Calcd for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>5</sub>S: C, 53.46; H, 4.98; N, 13.85. Found: C, 53.23;  
 H, 5.04; N, 13.62.

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Example 101

1      *Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-methylthiourea (2j).*

A solution of 2r (0.50 g, 2.26 mmol) and methyl isothiocyanate (0.20 g, 2.27 mmol) in THF (75 mL) was heated to reflux (4 h), and then the volatile materials were removed *in vacuo*. The residue was recrystallized from absolute EtOH to give 2j as a white solid (0.22 g, 33%): mp 162-163 °C (d);  $R_f$  0.45 (10% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400 (br), 3220 (br), 1620, 1500, 1430, 1340, 740 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.83 (s, C(O)CH<sub>3</sub>), 2.85 (br s, NHCH<sub>3</sub>), 4.27 (d,  $J$  = 5.8 Hz, CH<sub>2</sub>), 6.10 (br s, CH), 7.17-7.30 (m, 5PhH), 7.80 (br s, NH), 7.96 (br s, NH), 8.44 (br s, NH), 8.72 (s, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.39 (C(O)CH<sub>3</sub>), 30.92 (NHCH<sub>3</sub>), 42.45 (CH<sub>2</sub>), 61.33 (CH), 126.68 (C<sub>4'</sub>), 127.06 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.16 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 139.15 (C<sub>1'</sub>), 168.17 (C(O)NH), 170.03 (C(O)CH<sub>3</sub>) ppm, the signal for the thiocarbonyl carbon group was not detected.  
Mass spectrum (FD) 294 (M<sup>+</sup>).

Anal. Calcd for C<sub>13</sub>H<sub>18</sub>N<sub>4</sub>O<sub>2</sub>S: C, 53.04; H, 6.16; N, 19.03. Found: C, 53.16; H, 6.31; N, 18.89.

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Example 102

1        *Synthesis of 1-[Acetamido(benzylcarbamoyl)methyl]-3-phenylthiourea (2k).*

A solution of 2r (0.70 g, 3.16 mmol) and phenyl isothiocyanate (0.47 g, 3.48 mmol) in THF (75 mL) was heated to reflux (3 h), and then the volatile materials were  
5 removed *in vacuo*. The residue was triturated with EtOH (15 mL), and the white solid material (0.70 g, 62%) that remained was filtered and recrystallized from absolute EtOH: mp 196-197 °C (d);  $R_f$  0.65 (10% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400 (br), 3240 (br), 1620, 1470 (br), 1330, 750, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.89 (s, C(O)CH<sub>3</sub>), 4.32 (d,  $J$  = 5.8 Hz, CH<sub>2</sub>), 5.24 (t,  $J$  = 6.9 Hz, CH), 7.09-7.43 (m, 3ArH, 5PhH), 7.52-7.55 (m, 2ArH), 8.13 (d,  $J$  = 6.9 Hz, NH), 8.55 (br s, NH), 8.85 (br s, NH), 10.11 (s, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.22 (C(O)CH<sub>3</sub>), 42.36 (CH<sub>2</sub>), 61.18 (CH),  
10 122.76 (2C<sub>2</sub>), 124.29 (C<sub>4</sub>), 126.53 (C<sub>4'</sub>), 126.90 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.00 (2C<sub>2'</sub> or 2C<sub>3'</sub>),  
15 128.40 (2C<sub>3</sub>), 138.94 (C<sub>1</sub> or C<sub>1'</sub>), 139.01 (C<sub>1</sub> or C<sub>1'</sub>), 167.82 (C(O)NH), 169.98 (C(O)CH<sub>3</sub>), 180.02 (C(S)) ppm; mass spectrum (FD) 356 (M<sup>+</sup>).

Anal. Calcd for C<sub>18</sub>H<sub>20</sub>N<sub>4</sub>O<sub>2</sub>S: C, 60.65; H, 5.66; N, 15.72. Found: C, 60.43; H, 5.70; N, 15.62.

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Example 1031      *Synthesis of N-[Acetamido(benzylcarbamoyl)methyl]phthalamic acid (2l).*

To a warm pyridine solution (7.0 mL) containing 2r (0.63 g, 2.83 mmol), phthalic anhydride (0.43 g, 2.87 mmol) was added, and the reaction was stirred at 50-55 °C  
5 (5 h). Pyridine was removed by distillation *in vacuo* and the residue was treated with H<sub>2</sub>O (20 mL). The aqueous mixture was extracted with EtOAc (2 x 20 mL) and then acidified with aqueous 1 N HCl solution. The white solid (0.70 g, 70%) that precipitated was filtered, washed with H<sub>2</sub>O (10 mL), and dried: mp  
10 186-188 °C; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.90 (s, C(O)CH<sub>3</sub>), 4.36 (d, *J* = 6.0 Hz, CH<sub>2</sub>), 5.92 (t, *J* = 7.2 Hz, CH), 7.20-7.31 (m, 5PhH), 7.43 (d, *J* = 7.3 Hz, C<sub>6</sub>H), 7.50-7.63 (m, C<sub>4</sub>H, C<sub>5</sub>H), 7.82 (d, *J* = 7.3 Hz, C<sub>3</sub>H), 8.41-8.48 (m, 2NH), 9.01 (d, *J* = 7.2 Hz, NH), 13.30 (br s, CO<sub>2</sub>H); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.46 (C(O)CH<sub>3</sub>), 42.39 (CH<sub>2</sub>), 57.44 (CH), 126.57,  
15 126.92, 127.81, 128.09, 128.72, 129.36, 129.85, 131.49, 137.78, 138.99 (ArC, PhC), 167.85, 167.93, 168.48, 169.47 (C(O)) ppm; mass spectrum (FD) 370 (M<sup>++</sup>1).

Anal. Calcd for C<sub>19</sub>H<sub>19</sub>N<sub>3</sub>O<sub>5</sub>: C, 61.78; H, 5.18; N, 11.38. Found: C, 61.63;  
20 H, 5.05; N, 11.16.

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Example 104

1        *Synthesis of 2-Acetamido-N-benzyl-2-(N-succinimidyl)acetamide (2m).* A  
cooled (-78 °C) THF solution (150 mL) of 2s<sup>2</sup> (prepared from 2-acetamido-N-benzyl-  
2-ethoxyacetamide<sup>4,5</sup> (2.00 g, 8.0 mmol) and BBr<sub>3</sub> (2.51 g, 10.05 mmol)) was added  
5 slowly into a cooled (-78 °C) THF suspension (50 mL) of sodium succinimide (3.06  
g, 25.25 mmol). The reaction mixture was stirred at -78 °C (30 min) and at  
room temperature (90 min), and then treated with a 10% aqueous citric acid  
solution (50 mL). The resulting solution was neutralized with a saturated  
10 aqueous NaHCO<sub>3</sub> solution, and the reaction mixture extracted with EtOAc (3 × 100  
mL). The combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>), and the volatile materials were  
removed by distillation *in vacuo*. The residue was purified by flash column  
15 chromatography on SiO<sub>2</sub> gel (6% MeOH/CHCl<sub>3</sub>) to give 1.10 g (45%) of 2m: mp 181-  
183 °C (recrystallized from EtOH); R<sub>f</sub> 0.26 (6% MeOH/CHCl<sub>3</sub>); IR (KBr) 3340 (br),  
1620 (br), 1480 (br), 1340, 780, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.90 (s, C(O)CH<sub>3</sub>),  
2.67 (s, CH<sub>2</sub>CH<sub>2</sub>), 4.23-4.36 (m, CH<sub>2</sub>), 6.31 (d, *J* = 9.0 Hz, CH), 7.17-7.35 (m, 5 PhH),  
8.63 (t, *J* = 5.9 Hz, NH), 8.72 (d, *J* = 9.0 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.36  
20 (C(O)CH<sub>3</sub>), 27.99 (s, CH<sub>2</sub>CH<sub>2</sub>), 42.59 (CH<sub>2</sub>), 55.19 (CH), 126.63 (C<sub>4</sub>'), 126.96 (2C<sub>2</sub>' or  
2C<sub>3</sub>'), 128.08 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 138.91 (C<sub>1</sub>'), 165.41 (C(O)NH), 169.86 (C(O)CH<sub>3</sub>), 176.33  
(C(O)CH<sub>2</sub>CH<sub>2</sub>C(O)) ppm; mass spectrum (FAB) 304 (M<sup>+</sup>+1, 17), 163 (12), 155 (48),  
25 152 (51), 135 (68), 119 (100).

Anal. Calcd for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>: C, 59.40; H, 5.65; N, 13.85. Found: C, 59.63;  
H, 5.70; N, 13.66.

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Example 105

1      **Synthesis of Benzyl *N*-[Acetamido(benzylcarbamoyl)methyl]malonamate**  
 (2n). 4-Methylmorpholine (0.35 g, 3.56 mmol) was added to a solution of N-CBZ-  
 glycine (0.74 g, 3.55 mmol) in THF (75 mL) at -10 to -15 °C. The solution was  
 5 stirred (5 min), and then isobutylchloroformate (0.49 g, 3.55 mmol) was added and  
 the mixture was stirred for an additional 20 min. A cooled (-10 °C) solution of 2r  
 (0.79 g, 3.55 mmol) in THF (125 mL) was then added slowly (30 min). The reaction  
 mixture was stirred at this temperature (2 h) and then at room temperature (2 h).  
 10 The insoluble materials were filtered and the filtrate was concentrated *in vacuo*.  
 The residue was triturated with EtOAc (20 mL) and the white solid (0.60 g) that  
 remained was filtered, washed with H<sub>2</sub>O and dried to give 2n. The initial  
 insoluble material on trituration with H<sub>2</sub>O gave an additional 0.40 g of 2n to give a  
 15 combined yield of 1.00 g (68%); mp 177-179 °C (recrystallized from EtOH); R<sub>f</sub> 0.46  
 (10% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400 (br), 3260, 1640 (br), 1540 (br), 1480, 1450, 1370,  
 760, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.86 (s, C(O)CH<sub>3</sub>), 3.60-3.77 (m, C(O)CH<sub>2</sub>NH),  
 4.28 (d, *J* = 5.8 Hz, CH<sub>2</sub>), 5.01 (s, OCH<sub>2</sub>Ph), 5.79 (t, *J* = 7.7 Hz, CH), 7.18-7.34 (m, 5  
 20 PhH, 5 ArH), 7.49 (t, *J* = 5.8 Hz, NH), 8.43-8.55 (m, 3 × NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>)  
 22.36 (C(O)CH<sub>3</sub>), 42.28 (CH<sub>2</sub>), 43.39 (C(O)CH<sub>2</sub>NH), 56.77 (CH), 65.42 (OCH<sub>2</sub>Ph),  
 126.55 (2C), 126.94 (2C), 127.54, 127.66, 128.04 (2C), 128.22 (2C), 136.89, 138.96 (ArC,  
 PhC), 156.40 (NHC(O)OCH<sub>2</sub>Ph), 167.86 (NHC(O)CH<sub>2</sub>), 168.96 (C(O)NH), 169.30  
 25 (C(O)CH<sub>3</sub>) ppm; mass spectrum (FD) 413 (M<sup>+</sup>+1, 100), 278 (75).

Anal. Calcd for C<sub>21</sub>H<sub>24</sub>N<sub>4</sub>O<sub>5</sub>: C, 61.16; H, 5.87; N, 13.58. Found: C, 60.90;  
 H, 5.77; N, 13.35.

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Example 106

1        *Synthesis of Ethyl N-[Acetamido(benzylcarbamoyl)methyl]glycinate (2o). A*  
methanolic solution (70 mL) containing 2i (1.50 g, 4.28 mmol) and ethyl glycinate  
(prepared from ethyl glycinate hydrochloride (3.10 g, 22.2 mmol), NaOMe (1.17 g,  
5    21.74 mmol)) was heated to reflux (2h). The reaction was concentrated *in vacuo* to  
give an oily residue that was purified by flash column chromatography on SiO<sub>2</sub>  
gel (5% MeOH/CHCl<sub>3</sub>) to give 0.60 g (46%) of 2o: mp 125-127 °C (recrystallized from  
EtOAc); R<sub>f</sub> 0.43 (5% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400 (br), 3200, 1710, 1600, 1500, 1430,  
10    1350, 740, 680 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.17 (t, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.86 (s,  
C(O)CH<sub>3</sub>), 2.65-2.74 (m, NHCH<sub>2</sub>C(O)), 3.26-3.33 (m, NHCH<sub>2</sub>C(O)), 4.07 (q, *J* = 7.1  
Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.28 (d, *J* = 5.8 Hz, CH<sub>2</sub>), 5.01 (t, *J* = 8.2 Hz, CH), 7.19-7.35 (m, 5  
PhH), 8.25 (d, *J* = 8.2 Hz, NH), 8.58 (t, *J* = 5.8 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 13.98  
15    (OCH<sub>2</sub>CH<sub>3</sub>), 22.46 (C(O)CH<sub>3</sub>), 42.13 (CH<sub>2</sub>), 46.22 (NHCH<sub>2</sub>C(O)), 60.07 (OCH<sub>2</sub>CH<sub>3</sub>),  
63.96 (CH), 126.67 (C<sub>4</sub>'), 127.09 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.13 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 139.07 (C<sub>1</sub>'),  
169.07 (C(O)NH), 170.09 (C(O)CH<sub>3</sub>), 171.56 (C(O)OCH<sub>2</sub>CH<sub>3</sub>) ppm; mass spectrum  
(FD) 342 (M<sup>+</sup>).

20        Anal. Calcd for C<sub>15</sub>H<sub>21</sub>N<sub>3</sub>O<sub>4</sub>: C, 58.62; H, 6.89; N, 13.67. Found: C, 58.83;  
H, 7.00; N, 13.73.

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Example 1071      **Synthesis of Benzyl *N*-[Acetamido(benzylcarbamoyl)methyl]glycinate (2p).**

A suspension of benzyl glycinate hydrochloride (5.00 g, 24.8 mmol) in THF (400 mL) containing Et<sub>3</sub>N (4.90 g, 48.5 mmol) was stirred (4 h) at room temperature.

5 The reaction mixture was cooled (-78 °C) and then a cooled (-78 °C) THF solution (150 mL) of 2s (prepared from 2-acetamido-*N*-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol) and BBr<sub>3</sub> (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 20.0 mL, 20.0 mmol)) was added (30 min). The reaction mixture was stirred at -78 °C (30 min) and then at room temperature

10 (16 h). The insoluble materials were filtered, the filtrate concentrated *in vacuo*, and the residue was purified by flash column chromatography on SiO<sub>2</sub> gel (3% MeOH/CHCl<sub>3</sub>) to give 1.56 g (26%) of 2p as a white solid: mp 133-135 °C (recrystallized from EtOH); R<sub>f</sub> 0.36 (3% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400, 3220, 1710,

15 1620, 1510, 1440, 1350, 740, 680 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.85 (s, C(O)CH<sub>3</sub>), 2.71-2.82 (m, NHCH<sub>2</sub>C(O)), 3.39 (d, *J* = 6.1 Hz, NHCHHC(O)), 3.40 (d, *J* = 6.1 Hz, NHCHHC(O)), 4.27 (d, *J* = 6.1 Hz, CH<sub>2</sub>), 5.02 (t, *J* = 8.2 Hz, CH), 5.11 (s, OCH<sub>2</sub>Ph),

20 7.19-7.36 (m, 5 PhH, 5 ArH), 8.24 (d, *J* = 8.2 Hz, NH), 8.57 (t, *J* = 6.1 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.42 (C(O)CH<sub>3</sub>), 42.11 (CH<sub>2</sub>), 46.22 (NHCH<sub>2</sub>C(O)), 63.94 (CH), 65.53 (OCH<sub>2</sub>Ph), 126.62, 127.05 (2C), 127.80 (2C), 127.91, 128.08 (2C), 128.29 (2C), 135.87, 139.02 (ArC, PhC), 169.01 (C(O)NH), 170.06 (C(O)CH<sub>3</sub>), 171.45

25 (C(O)OCH<sub>2</sub>Ph) ppm; mass spectrum (FD) 370 (M<sup>+</sup>+1).

Anal. Calcd for C<sub>20</sub>H<sub>23</sub>N<sub>3</sub>O<sub>4</sub>: C, 65.03; H, 6.28; N, 11.37. Found: C, 65.15; H, 6.53; N, 11.31.

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Example 108

1        *Synthesis of N-[Acetamido(benzylcarbamoyl)methyl]glycine (2q).* A solution  
of methyl N-[acetamido(benzylcarbamoyl)methyl]glycinate (0.60 g, 2.05 mmol) and  
KOH (0.30 g, 5.36 mmol) in 90% aqueous EtOH (50 mL) was stirred at room  
5        temperature (48 h). The volatile materials were then removed *in vacuo*, and the  
residue dissolved in H<sub>2</sub>O (10 mL). The aqueous solution was extracted with EtOAc  
(2 x 20 mL), and the aqueous layer was acidified to pH ~2.0 with aqueous 1 N HCl.  
A column containing ion exchange resin Dowex 50X W4 was prepared using 10%  
10        aqueous pyridine. The column was thoroughly washed with H<sub>2</sub>O. The acidic  
aqueous reaction solution was added to the top of the column, and the column was  
eluted with H<sub>2</sub>O (300 mL) or until the eluate was neutral. The column was then  
eluted with 10% aqueous pyridine (400 mL). The aqueous pyridine fraction was  
15        concentrated *in vacuo* to give a white solid, dried *in vacuo*, and then triturated  
with absolute EtOH (7 mL). The insoluble materials that remained were filtered  
and dried to give 0.29 g (50%) of 2q: mp 124-126 °C (d); IR (KBr) 3400, 3200, 1630,  
1500, 1370, 690 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.84 (s, C(O)CH<sub>3</sub>), 3.26 (s, CH<sub>2</sub>C(O)),  
20        4.29 (d, *J* = 5.7 Hz, CH<sub>2</sub>), 4.98 (d, *J* = 8.2 Hz, CH), 7.21-7.33 (m, NH, 5 PhH), 8.39 (d,  
*J* = 8.2 Hz, NH), 8.47 (t, *J* = 5.7 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.41 (C(O)CH<sub>3</sub>),  
41.98 (CH<sub>2</sub>), 47.48 (CH<sub>2</sub>C(O)), 64.08 (CH), 126.75 (C<sub>4</sub>'), 127.21 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.24  
25        (2C<sub>2</sub>' or 2C<sub>3</sub>'), 139.23 (C<sub>1</sub>'), 169.91 (C(O)NH), 170.02 (C(O)CH<sub>3</sub>), 170.20 (CH<sub>2</sub>C(O))  
ppm.

Anal. Calcd for C<sub>13</sub>H<sub>17</sub>N<sub>3</sub>O<sub>4</sub>: C, 55.91; H, 6.13; N, 15.04. Found: C, 55.68;  
H, 6.06; N, 14.74.

Example 109

1        *Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrrole)acetamide.* A cooled (-78 °C)  
THF solution (225 mL) of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from  
2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and BBr<sub>3</sub> (1 M CH<sub>2</sub>Cl<sub>2</sub>  
5 solution, 8.8 mL, 8.8 mmol)) was added under N<sub>2</sub> to a cooled (-78 °C) suspension of  
potassium pyrrole (2.71 g, 25.8 mmol) in THF (25 mL). The reaction mixture was  
stirred at -78 °C (1 h) and then at room temperature (1 h), and then treated with  
H<sub>2</sub>O (10 mL) and acidified ("pH" 4.0) with 5% citric acid. The reaction was made  
10 basic with aqueous saturated Na<sub>2</sub>CO<sub>3</sub> solution, and the aqueous mixture was  
extracted with EtOAc (2 x 250 mL) and the combined organic layers were dried  
(Na<sub>2</sub>SO<sub>4</sub>). The volatile materials were removed *in vacuo* and the residue was  
purified by flash column chromatography on SiO<sub>2</sub> gel using 3% MeOH/CHCl<sub>3</sub> as  
15 the eluant to give 0.40 g (18%) of the desired product. The compound X was  
purified by recrystallization from EtOH: mp 182-184 °C; R<sub>f</sub> 0.44 (4%  
MeOH/CHCl<sub>3</sub>); IR (KBr) 3400, 3280, 1630, 1520, 1370, 740, 720 cm<sup>-1</sup>; <sup>1</sup>H NMR  
(DMSO-d<sub>6</sub>) δ 1.91 (s, C(O)CH<sub>3</sub>), 4.30 (d, *J* = 5.5 Hz, CH<sub>2</sub>), 6.01 (s, 2 x C<sub>3</sub>H), 6.38 (d, *J*  
20 = 8.7 Hz, CH), 6.85 (s, 2 x C<sub>2</sub>H), 7.11-7.35 (m, 5PhH), 8.96 (t, *J* = 5.5 Hz, NH), 9.14 (d,  
*J* = 8.7 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.22 (C(O)CH<sub>3</sub>), 42.15 (CH<sub>2</sub>), 62.86 (CH),  
107.79 (2C<sub>3</sub>), 119.19 (2C<sub>2</sub>), 126.76 (C<sub>4</sub>), 127.01 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.11 (2C<sub>2'</sub> or 2C<sub>3'</sub>),  
25 138.34 (C<sub>1</sub>), 166.37 (C(O)NH), 169.41 (C(O)CH<sub>3</sub>) ppm; mass spectrum, m/e (relative  
intensity) 272 (M<sup>++</sup>1, 22), 271 (M<sup>+</sup>, 100).

Anal. Calcd for C<sub>15</sub>H<sub>17</sub>N<sub>3</sub>O<sub>2</sub>·0.2 H<sub>2</sub>O: C, 65.53; H, 6.37; N, 15.28. Found: C,  
65.80; H, 6.22; N, 15.13.

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Example 110

1        *Synthesis of 2-Acetamido-N-benzyl-2-(1-pyrazole)acetamide.* To a cooled (-78  
 °C) solution (250 mL) of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from  
 2-acetamido-N-benzyl-2-ethoxyacetamide (3.60 g, 14.4 mmol) and BBr<sub>3</sub> (1 M  
 5 CH<sub>2</sub>Cl<sub>2</sub> solution, 15.8 mL, 15.8 mmol)), a THF solution (20 mL) of Et<sub>3</sub>N (2.91 g, 28.8  
 mmol) was added; followed by the addition of THF solution (30 mL) of pyrazole  
 (1.17 g, 17.28 mmol). The mixture was stirred at -78 °C (30 min) and room  
 temperature (1 h). The insoluble materials were filtered and the solvents removed  
 10 *in vacuo*. The residue was purified by flash column chromatography on SiO<sub>2</sub> gel  
 using 4% MeOH/CHCl<sub>3</sub> as the eluant to give 0.80 g (22%) of the desired product.  
 The compound X was recrystallized from EtOAc as a white solid: mp 158-160 °C;  
 R<sub>f</sub> 0.51 (6% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400, 3180, 1650, 1530, 1470, 1370, 1350, 740, 700  
 15 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.93 (s, C(O)CH<sub>3</sub>), 4.29 (d, *J* = 5.8 Hz, CH<sub>2</sub>), 6.26 (s,  
 C<sub>4</sub>H), 6.57 (d, *J* = 8.8 Hz, CH), 7.15-7.33 (m, 5PhH), 7.48 (br s, C<sub>5</sub>H), 7.76 (br s, C<sub>3</sub>H),  
 8.96 (t, *J* = 5.8 Hz, NH), 9.23 (d, *J* = 8.8 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.41  
 20 (C(O)CH<sub>3</sub>), 42.40 (CH<sub>2</sub>), 65.51 (CH), 105.37 (C<sub>4</sub>), 126.87 (C<sub>4'</sub>), 127.14 (2C<sub>2'</sub> or 2C<sub>3'</sub>),  
 128.25 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 129.00 (C<sub>5</sub>), 138.59 (C<sub>3</sub>), 139.17 (C<sub>1'</sub>), 165.68 (C(O)NH), 169.81  
 (C(O)CH<sub>3</sub>) ppm; mass spectrum, *m/e* (relative intensity) 273 (M<sup>++</sup>+1, 11), 272 (M<sup>+</sup>,  
 2), 139 (83), 138 (100), 92 (37).

25        Anal. Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95;  
 H, 5.96; N, 20.28.

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Example 111

1        *Synthesis of 2-Acetamido-N-benzyl-2-(1-imidazole)acetamide.* Using the  
preceeding procedure, 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0  
mmol), BBr<sub>3</sub> (1 M CH<sub>2</sub>Cl<sub>2</sub> solution, 8.8 mL, 8.8 mmol), Et<sub>3</sub>N (1.62 g, 1.60 mmol),  
5 and imidazole (0.60 g, 8.8 mmol) gave 0.60 g (30%) of the desired product.  
Compound X was recrystallized from ethyl acetate/hexane as a beige colored  
solid: mp 146-148 °C; R<sub>f</sub> 0. (7% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400 (br), 1640, 1560, 1480,  
1360, 720, 670 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.85 (s, C(O)CH<sub>3</sub>), 4.30 (br s, CH<sub>2</sub>), 6.53  
10 (d, *J* = 8.0 Hz, CH), 6.89 (s, C<sub>5</sub>H), 7.12-7.33 (m, C<sub>4</sub>H, 5PhH), 7.69 (s, C<sub>2</sub>H), 9.06 (br s,  
NH), 9.29 (d, *J* = 8.0 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.28 (C(O)CH<sub>3</sub>), 42.36 (CH<sub>2</sub>),  
61.18 (CH), 117.56 (C<sub>5</sub>), 126.92 (C<sub>4</sub>), 127.16 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.19 (C<sub>4</sub>), 128.26 (2C<sub>2</sub>' or  
2C<sub>3</sub>'), 136.21 (C<sub>2</sub>), 138.27 (C<sub>1</sub>'), 165.72 (C(O)NH), 169.77 (C(O)CH<sub>3</sub>) ppm; mass  
15 spectrum, FD (relative intensity) 274 (M<sup>++</sup>2, 12), 273 (M<sup>++</sup>1, 77), 272 (100), 205 (34),  
274 (18).

Anal. Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>: C, 61.75; H, 5.92; N, 20.57. Found: C, 61.95;  
20 H, 6.09; N, 20.32.

Example 112

1        *Synthesis of 2-Acetamido-N-benzyl-2-(1-(1,2,4-triazole))acetamide.* Using 2-  
acetamido-N-benzyl-2-ethoxyacetamide (4.00 g, 16.0 mmol), BBr<sub>3</sub> (1 M CH<sub>2</sub>Cl<sub>2</sub>  
solution, 17.6 mL, 17.6 mmol), Et<sub>3</sub>N (4.85 g, 48.0 mmol), and 1,2,4-triazole (1.43 g,  
5 20.8 mmol), 1.20 g (28%) of the desired product was obtained. Compound **X** was  
recrystallized from EtOAc as an amorphous white solid: mp 146-148 °C; R<sub>f</sub> 0.48  
(6% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400, 1660, 1470, 1370, 830 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ  
1.85 (s, C(O)CH<sub>3</sub>), 4.32 (br s, CH<sub>2</sub>), 6.70 (d, *J* = 7.8 Hz, CH), 7.21-7.29 (m, 5PhH),  
10 8.01 (s, C<sub>3</sub>H), 8.57 (s, C<sub>5</sub>H), 9.04 (br s, NH), 9.39 (d, *J* = 7.8 Hz, NH); <sup>13</sup>C NMR  
(DMSO-d<sub>6</sub>) 22.39 (C(O)CH<sub>3</sub>), 42.59 (CH<sub>2</sub>), 65.02 (CH), 126.97 (C<sub>4</sub>'), 127.25 (2C<sub>2</sub>' or  
2C<sub>3</sub>'), 128.32 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 138.47 (C<sub>1</sub>'), 143.93 (C<sub>5</sub>'), 151.50 (C<sub>3</sub>'), 164.77 (C(O)NH),  
15 170.23 (C(O)CH<sub>3</sub>) ppm; mass spectrum, FD (relative intensity) 274 (M<sup>+</sup>+1, 100), 273  
(11), 205 (19), 204 (13), 140 (67), 139 (31).

Anal. Calcd for C<sub>13</sub>H<sub>15</sub>N<sub>5</sub>O<sub>2</sub>: C, 57.13; H, 5.53; N, 25.63. Found: C, 57.37;  
H, 5.66; N, 25.38.

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Example 113

1        *Synthesis of 2-Acetamido-N-benzyl-2-(1-tetrazole)acetamide.* Making use of  
2-acetamido-N-benzyl-2-ethoxyacetamide (3.00 g, 12.0 mmol), BBr<sub>3</sub> (1 M CH<sub>2</sub>Cl<sub>2</sub>  
solution, 13.2 mL, 13.2 mmol), Et<sub>3</sub>N (2.42 g, 24.0 mmol), and tetrazole (1.10 g, 15.6  
5 mmol), 0.90 g (27%) of the desired product was obtained as a white solid. The  
compound X was recrystallized from EtOH: mp 169-171 °C; R<sub>f</sub> 0.22 (4%  
MeOH/CHCl<sub>3</sub>); IR (KBr) 3300 (br), 1660, 1510, 1360, 870, 740 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-  
d<sub>6</sub>) δ 1.97 (s, C(O)CH<sub>3</sub>), 4.25-4.40 (m, CH<sub>2</sub>), 7.05 (d, *J* = 8.4 Hz, CH), 7.21-7.38 (m,  
10 5PhH), 9.23 (t, *J* = 5.5 Hz, NH), 9.44 (s, C<sub>5</sub>H), 9.69 (d, *J* = 8.4 Hz, NH); <sup>13</sup>C NMR  
(DMSO-d<sub>6</sub>) 22.38 (C(O)CH<sub>3</sub>), 42.78 (CH<sub>2</sub>), 63.62 (CH), 127.10 (C<sub>4'</sub>), 127.39 (2C<sub>2'</sub> or  
2C<sub>3'</sub>), 128.38 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 138.26 (C<sub>1'</sub>), 143.67 (C<sub>5</sub>), 163.88 (C(O)NH), 170.62  
(C(O)CH<sub>3</sub>) ppm; mass spectrum, FD (relative intensity) 275 (M<sup>+</sup>, 79), 273 (14), 206  
15 (100), 205 (50).

Anal. Calcd for C<sub>12</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>: C, 52.55; H, 5.15; N, 30.64. Found: C, 52.75;  
H, 5.33; N, 30.64.

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Example 114

1        *Synthesis of  $\alpha$ -Acetamido-N-benzyl-1-(dimethylsulfamoyl)imidazole-4-*  
*acetamide.* To a cooled (-78 °C) THF solution (150 mL) of 2-acetamido-N-benzyl-2-  
bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g,  
5        8.0 mmol) and BBr<sub>3</sub> (1 M solution in CH<sub>2</sub>Cl<sub>2</sub>, 9.0 mL, 9.0 mmol)) was added Et<sub>3</sub>N  
(1.62 g, 16.0 mmol), and then a THF solution of the 2-lithio salt of N,N-  
dimethylimidazole-1-sulfonamide (generated by the addition of n-BuLi (2.5 M in  
hexane, 3.9 mL, 9.68 mmol) into a cooled (-78 °C) THF solution (25 mL) of N,N-  
10        dimethylimidazole-1-sulfonamide (1.54 g, 8.8 mmol)) was added during a 15 min  
interval. The reaction mixture was stirred at this temperature (30 min) and then  
at room temperature (45 min). A saturated aqueous NH<sub>4</sub>Cl solution (50 mL) and  
H<sub>2</sub>O (50 mL) were then successively added to the reaction, and the aqueous mixture  
15        was extracted with EtOAc (3 × 50 mL). The combined extracts were dried  
(Na<sub>2</sub>SO<sub>4</sub>), and the volatile materials were removed by distillation *in vacuo*. The  
residue was purified by flash column chromatography on SiO<sub>2</sub> gel (4%  
MeOH/CHCl<sub>3</sub>) to give 0.50 g (17%) of the desired product: mp 145-147 °C  
20        (recrystallized from EtOAc/hexane); R<sub>f</sub> 0.35 (4% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400,  
1640, 1530, 1380, 720 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.96 (s, C(O)CH<sub>3</sub>), 2.77 (s,  
N(CH<sub>3</sub>)<sub>2</sub>), 4.25 (dd, *J* = 6.0, 15.5 Hz, CHH), 4.34 (dd, *J* = 6.0, 15.5 Hz, CHH), 5.43 (d,  
*J* = 8.0, Hz, CH), 7.19-7.30 (m, 5 PhH), 7.40 (s, C<sub>5</sub>H), 8.17 (s, C<sub>2</sub>H), 8.42 (d, *J* = 8.0  
25        Hz, NH), 8.67 (t, *J* = 6.0 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.42 (C(O)CH<sub>3</sub>), 37.80  
(N(CH<sub>3</sub>)<sub>2</sub>), 42.11 (CH<sub>2</sub>), 51.40 (CH), 115.50 (C<sub>5</sub>), 126.64 (C<sub>4</sub>'), 126.94 (2C<sub>2</sub>' or 2C<sub>3</sub>'),  
128.12 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 136.70 (C<sub>2</sub>), 139.17 (C<sub>1</sub>'), 140.26 (C<sub>4</sub>), 168.93 (C(O)NH), 169.09  
30        (C(O)CH<sub>3</sub>) ppm; mass spectrum (FD) 380 (M<sup>+</sup>+1, 34), 248 (13), 247 (100), 108 (64).

Anal. Calcd for C<sub>16</sub>H<sub>21</sub>N<sub>5</sub>O<sub>4</sub>S: C, 50.65; H, 5.58; N, 17.87. Found: C, 51.92;  
H, 5.65; N, 18.09.

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Example 115

1        *Synthesis of  $\alpha$ -Acetamido-N-benzyl-4-imidazole acetamide.* A 75% aqueous  
EtOH (16 mL) solution of  $\alpha$ -acetamido-N-benzyl-1-(N,N-dimethylsulfamido)imida-  
zole-4-acetamide (0.85 g, 3.05 mmol) was acidified ("pH" ~1.5) with ethanolic HCl,  
5        and the solution was heated to reflux (8 h). The reaction was neutralized with a  
saturated aqueous NaHCO<sub>3</sub> solution and the EtOH-H<sub>2</sub>O azeotrope removed by  
distillation *in vacuo*. The remaining aqueous layer was made basic ("pH" 10)  
with aqueous NaOH. The aqueous mixture was extracted with EtOAc (3  $\times$  50 mL)  
10        and the combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>). The reaction was concentrated *in*  
*vacuo* to give 0.35 g (57%) of the desired product: mp 189-191 °C (d) (recrystallized  
from acetone); R<sub>f</sub> 0.19 (10% MeOH/CHCl<sub>3</sub>); IR (KBr) 3400, 3260, 1650, 1600, 1500,  
1430, 1360, 1330, 730, 710 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.88 (s, C(O)CH<sub>3</sub>), 4.28 (d, *J* =  
15        5.9 Hz, CH<sub>2</sub>), 5.38 (d, *J* = 6.8 Hz, CH), 5.38 (br s, C<sub>5</sub>H), 7.15-7.30 (m, 5 PhH), 7.60 (s,  
C<sub>2</sub>H), 8.26 (br s, NH), 8.53 (br s, NH), 12.01 (br s, NH) ppm; mass spectrum (FD)  
273 (M<sup>++1</sup>).

Anal. Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.59;  
20        H, 5.98; N, 20.37.

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Example 116Synthesis of  $\alpha$ -Acetamido-N-benzyl-2-imidazole acetamide.

Preparation of 1-diethoxymethyl-2-lithioimidazole. n-BuLi (2.5 M in hexane, 6.8 mL, 17.0 mmol) was added to a cooled (-46 °C) solution of 1-diethoxymethylimidazole (2.90 g, 17.06 mmol) in THF (45 mL) under N<sub>2</sub> atm. The solution was stirred at -46 °C (15 min) to give the desired product.

Preparation of  $\alpha$ -Acetamido-N-benzyl-2-imidazoleacetamide. The 2-lithio salt solution of 1-diethoxymethylimidazole was added dropwise (15 min) into a cooled (-78 °C) THF solution (130 mL) of 2-acetamido-N-benzyl-2-bromoacetamide (prepared from 2-acetamido-N-benzyl-2-ethoxyacetamide (2.00 g, 8.0 mmol) and BBr<sub>3</sub> (1 M in CH<sub>2</sub>Cl<sub>2</sub>, 10 mL, 10.0 mmol)). The reaction was stirred at -78 °C (1 h) and then quenched with a saturated aqueous NH<sub>4</sub>Cl (50 mL) solution. The mixture was stirred at room temperature (30 min), and made basic ("pH" 9.2) by adding aqueous K<sub>2</sub>CO<sub>3</sub>. The aqueous mixture was extracted with EtOAc (3  $\times$  100 mL), and the combined extracts were dried (Na<sub>2</sub>SO<sub>4</sub>). The solvents were removed *in vacuo* and the residue was purified by flash column chromatography on SiO<sub>2</sub> gel (2.5% MeOH/CHCl<sub>3</sub>) to give 0.14 g (7%) of the desired product: mp 228-230 °C (recrystallized from EtOH); R<sub>f</sub> 0.46 (10% MeOH/CHCl<sub>3</sub>); IR (KBr) 3200 (br), 1610, 1500 (br), 1430, 1350, 740, 680 cm<sup>-1</sup>; <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.91 (s, C(O)CH<sub>3</sub>), 4.29 (d, *J* = 5.6 Hz, CH<sub>2</sub>), 5.51 (d, *J* = 7.7 Hz, CH), 6.85 (br s, C<sub>4</sub>H), 7.05 (br s, C<sub>5</sub>H), 7.18-7.30 (m, 5 PhH), 8.42 (d, *J* = 7.7 Hz, NH), 8.65 (t, *J* = 5.6 Hz, NH), 11.91 (br s, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.49 (C(O)CH<sub>3</sub>), 42.21 (CH<sub>2</sub>), 51.62 (CH), 126.60 (C<sub>4</sub>'), 126.98 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 127.21 (C<sub>4</sub>), 128.09 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.32 (C<sub>5</sub>), 139.05 (C<sub>1</sub>'), 143.74 (C<sub>2</sub>), 168.12 (C(O)NH), 169.30 (C(O)CH<sub>3</sub>) ppm; mass spectrum (FD) 273 (M<sup>+</sup>+1, 65), 272 (M<sup>+</sup>, 100).

Anal. Calcd for C<sub>14</sub>H<sub>16</sub>N<sub>4</sub>O<sub>2</sub>: C, 61.75; H, 5.92; N, 20.58. Found: C, 61.56; H, 5.92; N, 20.37.

Example 117

1        *Synthesis of  $\alpha$ -Acetamido-N-benzyl-5-(tetrazole)acetamide.* A mixture of 2-  
 acetamido-N-benzyl-2-cyanoacetamide (1.00 g, 4.33 mmol), potassium azide (1.70  
 g, 20.96 mmol) and Et<sub>3</sub>N·HCl (1.78 g, 13.0 mmol) in 1-methyl-2-pyrrolidinone (125  
 5 mL) was stirred at 110 °C (7 h). After cooling, aqueous concentrated HCl (1 mL)  
 was added, and the reaction mixture was filtered. The solvent was removed *in*  
*vacuo*. The residue was dissolved in aqueous 1 N NaOH (20 mL), and then  
 aqueous 1 N HCl (20 mL) was added. The precipitate was filtered to give 0.77 g  
 10 (65%) of the desired product. The compound **X** was recrystallized from EtOH: mp  
 236-238 °C; R<sub>f</sub> 0.20 (30% MeOH/CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.94 (s, C(O)CH<sub>3</sub>),  
 4.33 (d, *J* = 5.7 Hz, CH<sub>2</sub>), 5.89 (d, *J* = 7.8 Hz, CH), 7.18-7.33 (m, 5 PhH), 8.86 (d, *J* =  
 7.8 Hz, NH), 8.92 (t, *J* = 5.7 Hz, NH), 16.54 (br s, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.21  
 15 (C(O)CH<sub>3</sub>), 42.37 (CH<sub>2</sub>), 48.13 (CH), 126.67 (C<sub>4'</sub>), 127.00 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.05 (2C<sub>2'</sub> or  
 2C<sub>3'</sub>), 138.52 (C<sub>1'</sub>), 166.18 (C(O)NH), 169.58 (C(O)CH<sub>3</sub>) ppm; mass spectrum, FD  
 (relative intensity) 275 (M<sup>+</sup>+1, 73), 274 (100). M<sub>r</sub> (+Cl) 274.119201 (calcd for  
 C<sub>12</sub>H<sub>14</sub>N<sub>6</sub>O<sub>2</sub>: 274.117824.

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Example 118

1        *Synthesis of  $\alpha$ -Acetamido-N-benzyl-3-(1,2,4-triazole)acetamide.* An  
ethanolic solution (250 mL) of 2-acetamido-N-benzyl-2-cyanoacetamide (3.00 g, 13.0  
mmol), formic hydrazide (1.60 g, 26.0 mmol) and  $K_2CO_3$  (6.00 g, 2.90 mmol) was  
5        heated at reflux (20h). The reaction mixture was allowed to cool, filtered, and  
the solvent was removed *in vacuo*. The residue was purified by flash column  
chromatography on  $SiO_2$  gel using 13% MeOH/ $CHCl_3$  as the eluant to give 1.40 g  
(40%) of the desired product. The compound **X** was purified by recrystallization  
10        from EtOH: mp 205-207 °C;  $R_f$  0.35 (16% MeOH/ $CHCl_3$ );  $^1H$  NMR ( $DMSO-d_6$ )  $\delta$  1.92  
(s,  $C(O)CH_3$ ), 4.30 (d,  $J = 5.7$  Hz,  $CH_2$ ), 5.62 (d,  $J = 7.8$  Hz, CH), 7.18-7.32 (m, 5  
PhH), 8.53 (s,  $C_5H$ ), 8.56 (d,  $J = 7.8$  Hz, NH), 8.71 (t,  $J = 5.7$  Hz, NH), 13.98 (s, NH);  
 $^{13}C$  NMR ( $DMSO-d_6$ ) 22.48 ( $C(O)CH_3$ ), 42.41 ( $CH_2$ ), 51.30 (CH), 126.63 ( $C_4'$ ), 127.08  
15        ( $2C_2'$  or  $2C_3'$ ), 128.11 ( $2C_2'$  or  $2C_3'$ ), 139.05 ( $C_1'$ ), 167.92 ( $C(O)NH$ ), 169.32 ( $C(O)CH_3$ )  
ppm; mass spectrum, FD (relative intensity) 274 ( $M^{++1}$ , 100), 273 (66).

Anal. Calcd for  $C_{13}H_{15}N_5O_2$ : C, 57.13; H, 5.53; N, 25.63. Found: C, 57.32;  
H, 5.57; N, 25.53.

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Example 119

1        *Synthesis of  $\alpha$ -Acetamido-N-benzyl-2-(carboxamide oxime)acetamide.* A  
suspension of  $\text{NH}_2\text{OH}\cdot\text{HCl}$  (1.80 g, 25.9 mmol),  $\text{K}_2\text{CO}_3$  (4.85 g, 35.0 mmol), 2-  
acetamido-N-benzyl-2-cyanoacetamide (2.00 g, 8.65 mmol) in absolute EtOH (150  
5 mL) was heated at reflux (16 h). The reaction mixture was cooled, filtered, and  
concentrated under vacuum. The residue was purified by flash column  
chromatography on  $\text{SiO}_2$  gel using 8% MeOH/ $\text{CHCl}_3$  as the eluant to give 1.24 g  
(54%) of the desired product. The compound X was further purified by  
10 recrystallization from ethyl acetate/hexane: mp 172-173 °C;  $R_f$  0.40 (10%  
MeOH/ $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{DMSO-d}_6$ )  $\delta$  1.87 (s,  $\text{C(O)CH}_3$ ), 4.27 (d,  $J = 6.0$  Hz,  $\text{CH}_2$ ),  
4.88 (d,  $J = 8.4$  Hz, CH), 5.37 (s,  $\text{NH}_2$ ), 7.21-7.30 (m, 5 PhH), 8.21 (d,  $J = 8.4$  Hz, NH),  
8.48 (t,  $J = 6.0$  Hz, NH), 9.28 (s, OH);  $^{13}\text{C}$  NMR ( $\text{DMSO-d}_6$ ) 22.46 ( $\text{C(O)CH}_3$ ), 42.15  
15 ( $\text{CH}_2$ ), 53.65 (CH), 126.60 ( $\text{C}_4'$ ), 126.99 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ), 128.108 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ), 139.02  
( $\text{C}_1'$ ), 149.63 ( $\text{CNH}_2$ ), 167.88 ( $\text{C(O)NH}$ ), 169.07 ( $\text{C(O)CH}_3$ ) ppm; mass spectrum, FD  
(relative intensity) 265 ( $\text{M}^++1$ , 36), 264 (100).

Anal. Calcd for  $\text{C}_{12}\text{H}_{16}\text{N}_4\text{O}_3$ : C, 54.54; H, 6.10; N, 21.20. Found: C, 54.81;  
20 H, 6.01; N, 21.41.

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Example 120

1        *Synthesis of  $\alpha$ -Acetamido-N-benzyl-2-(carboxamide oxime-(O-acetate))-*  
*acetamide.* To a stirred solution of  $\alpha$ -acetamido-N-benzyl-2-(carboxamide  
 5    *oxime)acetamide* (0.72 g, 7.25 mmol) in pyridine (8 mL), acetyl chloride (0.25 mL,  
*X* mmol) was added dropwise. Upon addition of the acetyl chloride a small  
 exotherm was detected (25 °C to 37 °C). The reaction mixture was stirred at room  
 temperature (1 h). The solvent was then removed *in vacuo*, and the residue was  
 dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The solution was washed with an aqueous 0.5 N  
 10    HCl solution (20 mL). The organic phase was dried (Na<sub>2</sub>SO<sub>4</sub>), and the solvent was  
 removed *in vacuo* to give 0.60 g (72%) of the desired product. The compound **X** was  
 recrystallized from chloroform/hexane: mp 131-133 °C; R<sub>f</sub> 0.35 (4%  
 15    MeOH/CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$  1.90 (s, C(O)CH<sub>3</sub>), 2.06 (s, OC(O)CH<sub>3</sub>), 4.29 (t,  
*J* = 5.3 Hz, CH<sub>2</sub>), 5.00 (d, *J* = 8.4 Hz, CH), 6.48 (br s, NH<sub>2</sub>), 7.19-7.33 (m, 5 PhH), 8.29  
 (d, *J* = 8.4 Hz, NH), 8.66 (t, *J* = 5.3 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 19.86 (OC(O)CH<sub>3</sub>),  
 22.77 (C(O)CH<sub>3</sub>), 42.50 (CH<sub>2</sub>), 53.45 (CH), 126.89 (C<sub>4'</sub>), 127.28 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 128.38  
 20    (2C<sub>2'</sub> or 2C<sub>3'</sub>), 139.00 (C<sub>1'</sub>), 156.13 (CNH<sub>2</sub>), 167.19 (C(O)NH), 168.49 (OC(O)CH<sub>3</sub>),  
 169.55 (C(O)CH<sub>3</sub>) ppm; mass spectrum, FD (relative intensity) 307 (M<sup>+</sup>+1, 100), 306  
 (43).

Anal. Calcd for C<sub>14</sub>H<sub>18</sub>N<sub>4</sub>O<sub>4</sub>: C, 54.89; H, 5.92; N, 18.29. Found: C, 54.86;  
 25    H, 5.84; N, 18.19.

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Example 121

1        *Synthesis of  $\alpha$ -Acetamido-N-benzyl-3-(1,2,4-oxadiazole)acetamide.*  $\alpha$ -  
Acetamido-N-benzyl-2-(carboxamide oxime)acetamide (0.90 g, 3.4 mmol) was  
dissolved in trimethylorthoformate (10 mL) containing  $\text{BF}_3 \cdot \text{Et}_2\text{O}$  (6 drops). The  
5 solution was warmed to 55 °C (20 min), and then evaporated under reduced  
pressure to give a white-blue solid. The material was dissolved in MeOH and  
treated with norit, filtered, and evaporated under reduced pressure to furnish  
crude product (0.79 g, 85%). The compound was purified by recrystallization from  
10 chloroform/hexane: mp 164-166 °C;  $R_f$  0.37 (6% MeOH/ $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.92 (s,  $\text{C}(\text{O})\text{CH}_3$ ), 4.31 (d,  $J = 6.0$  Hz,  $\text{CH}_2$ ), 5.82 (d,  $J = 8.4$  Hz, CH), 7.15-7.34  
(m, 5 PhH), 8.88 (d,  $J = 8.4$  Hz, NH), 8.96 (t,  $J = 6.0$  Hz, NH), 9.62 (s,  $\text{C}_5\text{H}$ );  $^{13}\text{C}$  NMR  
( $\text{DMSO}-d_6$ ) 22.22 ( $\text{C}(\text{O})\text{CH}_3$ ), 42.35 ( $\text{CH}_2$ ), 49.44 (CH), 126.77 ( $\text{C}_4'$ ), 127.06 ( $2\text{C}_2'$  or  
15  $2\text{C}_3'$ ), 128.18 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ), 138.70 ( $\text{C}_1'$ ), 166.25 ( $\text{C}(\text{O})\text{NH}$ ), 166.74 ( $\text{C}_3$ ), 167.24  
( $\text{C}(\text{O})\text{CH}_3$ ), 169.52 ( $\text{C}_5$ , CH) ppm; mass spectrum, FD (relative intensity) 275  
( $\text{M}^++1$ , 28), 274 (100).

20        Anal. Calcd for  $\text{C}_{13}\text{H}_{14}\text{N}_4\text{O}_3$ : C, 56.93; H, 5.14; N, 20.43. Found: C, 56.65;  
H, 5.01; N, 20.28.

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Example 122

1        *Synthesis of  $\alpha$ -Acetamido-N-benzyl-2-(thioamide)acetamide.* 2-Acetamido-  
N-benzyl-2-cyanoacetamide (4.00 g, 34.64 mmol) and O,O-diethyldithiophosphoric  
acid (6.45 g, 34.64 mmol) were dissolved in a binary MeOH (80 mL)-EtOH (80 mL)  
5 solution containing H<sub>2</sub>O (0.32 mL) and heated at 70 °C (6 h) and then allowed to  
remain at room temperature (13 h). The reaction mixture was filtered, and the  
solvent was removed *in vacuo*. The residue was triturated with EtOAc to give 2.00  
g (44%) of the desired compound. The thioamide was recrystallized from ethyl  
10 acetate/hexane: mp 170-171 °C; R<sub>f</sub> 0.51 (8% MeOH/CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>)  $\delta$   
1.93 (s, C(O)CH<sub>3</sub>), 4.29 (d, *J* = 5.0 Hz, CH<sub>2</sub>), 5.21 (d, *J* = 8.0 Hz, CH), 7.15-7.31 (m, 5  
PhH), 8.03 (d, *J* = 8.0 Hz, NH), 8.69 (t, *J* = 5.0 Hz, NH), 9.27 (s, NHH'), 9.91 (s,  
15 NHH'); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.68 (C(O)CH<sub>3</sub>), 42.24 (CH<sub>2</sub>), 62.95 (CH), 126.63 (C<sub>4</sub>'),  
126.96 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.087 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 138.83 (C<sub>1</sub>'), 166.42 (C(O)NH), 169.10  
(C(O)CH<sub>3</sub>), 200.28 (C(S)NH<sub>2</sub>) ppm; mass spectrum, FD (relative intensity) 266  
(M<sup>+</sup>+1, 42), 265 (100).

20        Anal. Calcd for C<sub>12</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>S: C, 54.32; H, 5.70; N, 15.84. Found: C, 54.44;  
H, 5.74; N, 15.54.

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Example 123

1        *Synthesis of Ethyl 2-Acetamido-2-vinylacetate.* Vinyl magnesium bromide  
(10.9 mL, 1 N, 10.9 mmol) was slowly added to a cooled (-78 °C) solution of ethyl 2-  
acetamido-2-bromoacetate (1.10 g, 4.91 mmol) in THF (50 mL). The reaction was  
5 stirred at -78 °C (2 h), and was then quenched with a 1 N citric acid solution (7.0  
mL). The mixture was allowed to warm to room temperature, and then the THF  
was removed *in vacuo*. The aqueous mixture was extracted with CHCl<sub>3</sub> (3 x 100  
mL), and the combined CHCl<sub>3</sub> extracts were dried (Na<sub>2</sub>SO<sub>4</sub>) and concentrated to  
10 dryness. The residue was purified by flash chromatography using SiO<sub>2</sub> gel and  
2% MeOH/CHCl<sub>3</sub> as the eluant to give 0.50 g (60%) of the desired product as a light  
yellow colored oil: R<sub>f</sub> 0.51 (4% MeOH/CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.17 (t, *J* = 7.1  
Hz, OCH<sub>2</sub>CH<sub>3</sub>), 1.88 (s, C(O)CH<sub>3</sub>), 4.09 (d, *J* = 7.1 Hz, OCH<sub>2</sub>CH<sub>3</sub>), 4.80-4.86 (m, α-  
15 CH), 5.22-5.35 (m, CH=CH<sub>2</sub>), 5.82-5.92 (m, CH=CH<sub>2</sub>), 8.47 (d, *J* = 7.4 Hz, NH); <sup>13</sup>C  
NMR (DMSO-d<sub>6</sub>) 13.96 (OCH<sub>2</sub>CH<sub>3</sub>), 22.12 (C(O)CH<sub>3</sub>), 54.65 (α-CH), 60.71  
(OCH<sub>2</sub>CH<sub>3</sub>), 117.89 (CH=CH<sub>2</sub>), 132.48 (CH=CH<sub>2</sub>), 169.16 (C(O)CH<sub>3</sub>), 170.26  
20 (C(O)NH) ppm.

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Example 124

1        *Synthesis of Vinyl Glycine.* A mixture of ethyl 2-acetamido-2-vinyl acetate  
(5.20 g, 30.40 mmol) and aqueous 6 N HCl (200 mL) was heated to reflux (2 h). The  
mixture was cooled to room temperature, and then extracted with  $\text{CHCl}_3$  (3 x 100  
5 mL). The aqueous solution which was dark brown in color was decolorized with  
norit (15 min) at 60 °C, and then the mixture was filtered, and the filtrate was  
concentrated to dryness to give crude vinyl glycine hydrochloride. The salt was  
dissolved in a minimum amount of  $\text{H}_2\text{O}$  and acidified to pH 2.0 with aqueous 1 N  
10 HCl. The solution was applied to an ion exchange resin (Dowex 50XW4,  
ammonium form) and eluted with  $\text{H}_2\text{O}$  until the eluate was neutral. The ion  
exchange column was then eluted with an aqueous 1 N  $\text{NH}_4\text{OH}$  solution (~500  
mL). Removal of volatile materials from the  $\text{NH}_4\text{OH}$  eluate gave 1.80 g (60%) of  
15 vinyl glycine: mp 218-220 °C (d);  $^1\text{H}$  NMR ( $\text{D}_2\text{O}$ )  $\delta$  4.09 (d,  $J = 7.2$  Hz,  $\alpha\text{-CH}$ ), 5.28-  
5.35 (m,  $\text{CH}=\text{CH}_2$ ), 5.80-5.87 (m,  $\text{CH}=\text{CH}_2$ ).

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Example 125

1        *Synthesis of 2-Acetamido-2-vinylacetic acid.* Acetic anhydride (2.50 g, 24.50  
mmol) was added slowly into a cooled (-10 °C) solution of vinyl glycine (2.20 g, 21.78  
mmol) in AcOH (100 mL). The mixture was stirred at this temperature (30 min)  
5 and then at room temperature (3 h). The solution was concentrated repeatedly  
from H<sub>2</sub>O. The residue was dissolved in absolute EtOH (200 mL) and then  
decolorized (norit, 60 °C), and filtered. The filtrate was concentrated *in vacuo*,  
and the residue was triturated with Et<sub>2</sub>O to give 1.70 g (55%) of the desired product  
10 as a low melting yellow solid: <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.87 (s, C(O)CH<sub>3</sub>), 4.75 (dd, *J* =  
6.2, 7.5 Hz, α-CH), 5.13-5.27 (m, CH=CH<sub>2</sub>), 5.84-5.96 (m, CH=CH<sub>2</sub>), 8.24 (d, *J* = 7.5  
Hz, NH).

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Example 126

*Synthesis of 2-Acetamido-N-benzyl-2-vinylacetamide.* 4-Methyl morpholine (0.71 g, 6.99 mmol) was added to a suspension of 2-acetamido-2-vinylacetic acid (1.00 g, 6.99 mmol) in THF (325 mL), and the mixture was stirred at room temperature (30 min). The reaction was cooled to -10 to -15 °C and then isobutylchloroformate (1.24 g, 9.08 mmol) was then added dropwise. After stirring (10 min), a solution of benzylamine (0.75 g, 6.99 mmol) in THF (25 mL) was added (15 min). The reaction mixture was allowed to warm to 0 °C. The insoluble material was filtered. The filtrate was concentrated *in vacuo*, and the residue was purified by flash column chromatography on SiO<sub>2</sub> gel using 3% MeOH/CHCl<sub>3</sub> as the eluant to give 1.00 g (62%) of the desired product: mp 136-138 °C (recrystallized from EtOAc); R<sub>f</sub> 0.24 (3% MeOH/CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.88 (s, C(O)CH<sub>3</sub>), 4.27 (d, *J* = 5.6 Hz, CH<sub>2</sub>), 4.89-4.94 (dd, *J* = 6.4, 7.8 Hz, α-CH), 5.13-5.30 (m, -CH=CH<sub>2</sub>), 5.81-5.93 (m, -CH=CH<sub>2</sub>), 7.20-7.33 (m, 5 PhH), 8.27 (d, *J* = 7.8 Hz, NH), 8.58 (t, *J* = 5.6 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.47 (C(O)CH<sub>3</sub>), 42.05 (CH<sub>2</sub>), 55.24 (α-CH), 116.44 (CH=CH<sub>2</sub>), 126.74 (C<sub>4</sub>'), 127.05 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 128.24 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 134.76 (CH=CH<sub>2</sub>), 139.25 (C<sub>1</sub>'), 168.78 (C(O)CH<sub>3</sub>), 168.99 (C(O)NH) ppm.

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Example 127

1        **Synthesis of 2-Acetamido-N-benzyl-2-epoxyacetamide.** A solution of 2-  
 5 acetamido-N-benzyl-2-vinylacetamide (1.00 g, 4.31 mmol) and m-chloroperoxy-  
 benzoic acid (1.76 g, 55%, 5.60 mmol) in dichloromethane (100 mL) was stirred at  
 room temperature (24 h), and then heated at reflux (3 h). The reaction solution  
 was treated with a saturated aqueous Na<sub>2</sub>SO<sub>3</sub> solution (20 mL) and then the  
 organic layer was extracted with a saturated aqueous NaHCO<sub>3</sub> solution (3 x 50  
 10 mL). The organic layer was washed with a saturated aqueous NaCl solution and  
 dried (Na<sub>2</sub>SO<sub>4</sub>). The CH<sub>2</sub>Cl<sub>2</sub> was removed *in vacuo*, and the residue was then  
 purified by flash column chromatography on SiO<sub>2</sub> gel using 4% MeOH/EtOAc as  
 the eluant to give 0.35 g (33%) of the desired product: mp °C (recrystallized from  
 15 EtOAc); R<sub>f</sub> 0.48 (5% MeOH/CHCl<sub>3</sub>); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 1.87 (s, C(O)CH<sub>3</sub>), 2.66  
 (dd, *J* = 2.5, 5.0 Hz, CH(O)CHH), 2.75 (dd, *J* = 4.3, 5.0 Hz, CH(O)CHH), 3.20 (m,  
 CH(O)CHH), 4.25-4.32 (m, α-CH, CH<sub>2</sub>), 7.21-7.34 (m, 5 PhH), 8.30 (d, *J* = 8.1 Hz,  
 NH), 8.59 (t, *J* = 5.8 Hz, NH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.18 (C(O)CH<sub>3</sub>), 41.99 (CH<sub>2</sub>),  
 20 43.91 (CH(O)CH<sub>2</sub>), 51.30 (CH(O)CH<sub>2</sub>), 53.80 (α-CH), 126.49 (C<sub>4</sub>'), 126.83 (2C<sub>2</sub>' or  
 2C<sub>3</sub>'), 127.98 (2C<sub>2</sub>' or 2C<sub>3</sub>'), 138.86 (C<sub>1</sub>'), 168.52 (C(O)NH), 169.24 (C(O)CH<sub>3</sub>) ppm.

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Example 128

1        *Synthesis of Potassium 2-Acetamido-N-benzylacetamide-2-sulfonate.* A  
solution of 2-acetamido-N-benzyl-2-(trimethylammonium)acetamide tetrafluoro-  
borate (0.30 g, 0.85 mmol) and K<sub>2</sub>SO<sub>3</sub> (0.68 g, 4.26 mmol) in H<sub>2</sub>O (7.0 mL) was  
5 heated at 50-55 °C (4 h). The solution was evaporated to dryness, and the residue  
was extracted with hot MeOH (3 x 10 mL). The MeOH was removed *in vacuo* to  
give a white solid (~30 mg): <sup>1</sup>H NMR (D<sub>2</sub>O) δ 1.97 (s, C(O)CH<sub>3</sub>), 4.33 (CH<sub>2</sub>), 5.45  
(CH), 7.19-7.28 (m, 5 PhH); <sup>13</sup>C NMR (D<sub>2</sub>O) 22.00 (C(O)CH<sub>3</sub>), 43.41 (CH<sub>2</sub>), 67.77  
10 (CH), 127.18 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 127.53 (C<sub>4'</sub>), 128.83 (2C<sub>2'</sub> or 2C<sub>3'</sub>), 137.58 (C<sub>1'</sub>), 166.02  
(C(O)NH), 173.65 (C(O)CH<sub>3</sub>) ppm.

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Example 129

1        **Synthesis of Ethyl 2-Acetamido-4-pentenoic acid ester.** Allyltrimethyl-  
silane (4.09 g, 31.40 mmol) was added to a stirred solution of ethyl 2-acetamido-2-  
bromoacetate (1.76 g, 7.86 mmol) in dry THF (90 mL). After stirring (5 min), an  
5        ethereal solution of  $\text{ZnCl}_2$  (1 N, 12.2 mL, 12.2 mmol) was added and the stirring  
was continued (70 h). The THF was removed by distillation *in vacuo* and the  
residue that remained was treated with  $\text{H}_2\text{O}$  (50 mL). The aqueous mixture was  
extracted with  $\text{CH}_2\text{Cl}_2$  ( $3 \times 75$  mL), the combined extract was dried ( $\text{Na}_2\text{SO}_4$ ) and  
10        concentrated to give 1.40 g (97%) of the desired product. The ester was purified by  
distillation *in vacuo* (65-70 °C, 0.3-0.8 torr) to give the desired product as a colorless  
oil:  $R_f$  0.35 (3% MeOH/ $\text{CHCl}_3$ );  $^1\text{H}$  NMR ( $\text{CDCl}_3$ )  $\delta$  1.25 (t,  $J = 6.8$  Hz,  $\text{OCH}_2\text{CH}_3$ ),  
1.99 (s,  $\text{C(O)CH}_3$ ), 2.44-2.60 (m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.17 (q,  $J = 6.8$  Hz,  $\text{OCH}_2\text{CH}_3$ ), 4.60-  
15        4.66 (m, CH), 5.07-5.11 (m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.59-5.70 (m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 6.15 (br s,  
NH);  $^{13}\text{C}$  NMR ( $\text{CDCl}_3$ ) 14.09 ( $\text{OCH}_2\text{CH}_3$ ), 23.00 ( $\text{C(O)CH}_3$ ), 36.46 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ),  
51.58 (CH), 61.39 ( $\text{OCH}_2\text{CH}_3$ ), 118.95 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 132.15 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 169.64  
20        ( $\text{C(O)CH}_3$ ), 171.74 ( $\text{C(O)OCH}_2\text{CH}_3$ ) ppm; mass spectrum, m/e (relative intensity)  
186 ( $\text{M}^++1$ , 2), 144 (19), 126 (7), 112 (31), 102 (73), 87 (18), 71 (100), 70 (89).

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Example 130

1        *Synthesis of 2-Acetamido-4-pentenoic acid.* Ethyl 2-acetamido-4-pentenoic  
acid ester (1.20 g, 6.50 mmol) was dissolved in 90:5 EtOH:H<sub>2</sub>O (40 mL), and then  
KOH (1.50 g, 26.80 mmol) was added and the resulting solution stirred at room  
5        temperature (48 h). The reaction was concentrated *in vacuo* and the residue  
diluted with H<sub>2</sub>O (15 mL) and then washed with Et<sub>2</sub>O (2 × 30 mL). The aqueous  
layer was then made acidic with 8.5% H<sub>3</sub>PO<sub>4</sub> and extracted with EtOAc (3 × 75  
mL). The combined organic layers were dried (Na<sub>2</sub>SO<sub>4</sub>), and evaporated *in vacuo*  
10        to give 0.56 g (55%) of the desired product: mp 113-115 °C (recrystallized from  
EtOAc); <sup>1</sup>H NMR (DMSO-d<sub>6</sub>) δ 2.00 (C(O)CH<sub>3</sub>), 2.43-2.65 (m, CH<sub>2</sub>CH=CH<sub>2</sub>), 4.36-  
4.43 (m, CH), 5.19-5.30 (m, CH<sub>2</sub>CH=CH<sub>2</sub>), 5.84-5.98 (m, CH<sub>2</sub>CH=CH<sub>2</sub>), 8.29 (d, *J* =  
7.7 Hz, NH), 12.78 (br s, OH); <sup>13</sup>C NMR (DMSO-d<sub>6</sub>) 22.35 (C(O)CH<sub>3</sub>), 35.44  
15        (CH<sub>2</sub>CH=CH<sub>2</sub>), 51.68 (CH), 117.70 (CH<sub>2</sub>CH=CH<sub>2</sub>), 134.07 (CH<sub>2</sub>CH=CH<sub>2</sub>), 169.27  
(C(O)CH<sub>3</sub>), 173.11 (CO<sub>2</sub>H) ppm; mass spectrum, *m/e* (relative intensity) 158 (M<sup>+</sup>+1,  
2), 139 (6), 116 (20), 112 (8), 74 (73), 70 (47), 42 (100).

20        Anal. Calcd for C<sub>7</sub>H<sub>11</sub>NO<sub>3</sub>: C, 53.50; H, 7.06; N, 8.91. Found: C, 53.64; H,  
7.15; N, 8.82.

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Example 131

1        *Synthesis of 2-Acetamido-4-pentenoic acid-N-benzylamide.* 4-Methylmor-  
 pholine (0.55 g, 5.40 mmol) was added to a cooled (-10 to -15 °C) THF solution (60  
 mL) of 2-acetamido-4-pentenoic acid (0.81 g, 5.18 mmol), and then isobutylchloro-  
 5        formate (0.75 g, 5.70 mmol) was added leading to the precipitation of a white solid.  
 After 2 min, a solution of benzylamine (0.61 g, 5.70 mmol) in THF (10 mL) was  
 slowly added at -10 to -15 °C. The reaction was allowed to warm (5 min) at room  
 temperature and the insoluble salts were removed by filtration, and the filtrate  
 10        was evaporated to dryness. The residue was triturated with EtOAc (10 mL), and  
 the remaining white solid was filtered to give 0.81 g (64%) of the desired product:  
 mp 118-120 °C (recrystallized from ethyl acetate/cyclohexane);  $R_f$  0.36 (4%  
 MeOH/ $\text{CHCl}_3$ ); IR (KBr) 3200 (br), 3040, 2900, 1650 (br), 1540 (br), 1350, 750, 700  
 15         $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR ( $\text{DMSO}-d_6$ )  $\delta$  1.83 (s,  $\text{C}(\text{O})\text{CH}_3$ ), 2.22-2.49 (m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 4.26 (d,  
 $J = 5.3$  Hz,  $\text{CH}_2\text{Ph}$ ), 4.25-4.33 (m, CH), 4.99-5.09 (m,  $\text{CH}_2\text{CH}=\text{CH}_2$ ), 5.65-5.77 (m,  
 $\text{CH}_2\text{CH}=\text{CH}_2$ ), 7.21-7.29 (m, 5 PhH), 8.05 (d,  $J = 7.6$  Hz, NH), 8.46 (br s, NH);  $^{13}\text{C}$   
 20        NMR ( $\text{DMSO}-d_6$ ) 22.41 ( $\text{C}(\text{O})\text{CH}_3$ ), 36.24 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 41.91 ( $\text{CH}_2\text{Ph}$ ), 52.20 (CH),  
 117.15 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 126.54 ( $\text{C}_4'$ ), 126.99 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ), 128.04 ( $2\text{C}_2'$  or  $2\text{C}_3'$ ), 139.22  
 (C $_1'$ ), 134.25 ( $\text{CH}_2\text{CH}=\text{CH}_2$ ), 169.02 ( $\text{C}(\text{O})\text{CH}_3$ ), 170.96 ( $\text{C}(\text{O})\text{NH}$ ) ppm; mass  
 spectrum,  $m/e$  (relative intensity) 246 ( $\text{M}^+$ , 4), 205 (4), 163 (15), 140 (8), 106 (33), 91  
 25        (77), 70 (100).

Anal. Calcd for  $\text{C}_{14}\text{H}_{18}\text{N}_2\text{O}_2$ : C, 68.27; H, 7.37; N, 11.37. Found: C, 68.55;  
 H, 7.31; N, 11.48.

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Example 132

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Using the procedures described herein, the following compounds can also be synthesized:

$\alpha$ -acetamido-N-benzyl-2-(2-oxazole)-acetamide

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$\alpha$ -acetamido-N-benzyl-2-(2-thiazole)-acetamide.

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1      Pharmacology. Using male Carworth Farms #1 mice,  
compounds of the present invention were tested for anti-  
convulsant activity according to the following procedure:

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1 In the rotorod test, the animal was placed on a  
one-inch diameter knurled plastic rod rotating  
at 6 rpm after the administration of the drug. Normal  
mice can remain on a rod rotating at this speed indefinitely.

5 Neurologic toxicity was defined as the failure of the  
animal to remain on the rod for one minute. In the  
horizontal screen test, previously trained mice were  
dosed with the compound and placed individually on  
top of a square (13 cm X 13 cm) wire screen (no. 4  
10 mesh) which was mounted on a metal rod. The rod was  
rotated 180°, and the number of mice that returned  
to the top of the screen was determined. Inability  
to climb to the top within one minute was defined as  
"neurological impairment". This procedure is described  
15 in Pharmacol. Biochem. Behav. 6, 351-353 (1977) and  
is incorporated herein by reference with the same force  
and effect as if fully set forth herein.

The dose effect behavior of the compounds was evaluated using  
the above-described procedures by the administration  
20 of varying dose levels, treating normally eight mice  
at each dose. Table I includes an evaluation of the  
Median Effective Dose (ED50) and the Median Toxic Dose  
(TD50) of representative compounds. Mice were tested  
25 with varying doses of the anticonvulsant to define  
the limits of complete protection (or toxicity) and  
no protection (or no toxicity), as well as three points  
in between these limits. The Median Effective Dose  
(ED50) was defined as the dose which produced the desired  
30 endpoint in 50% of the animals. The Median Toxicity  
Dose (TD50) was the dose which elicited evidence of  
minimal neurological toxicity in 50% of the animals.

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More specifically, data tabulated in Table 1 were generated as follows:

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The compound was given in various dose levels (i.e., 10, 30, 100, 300 mg) and subsequently compared with phenytoin, phenobarbital, mephentyoin and phenacemide (See Table I). N-Acetyl-D,L-alanine-N'-benzylamide was tested at 600 mg/mL as well. Seizures were then artificially induced by either electroschock or pentylenetetrazole. Maximal electroshock seizures (MES) were elicited with a 60 cycle alternating current of 50mA intensitiy (5-7 times that necessary to elicit minimal electroshock seizures) delivered for 0.2 sec via corneal electrodes. A drop of 0.9% saline was instilled in the eye prior to application of the electrodes so as to prevent the death of the animal. Protection in this test was defined as the abolition of the hind limb tonic extension component of the seizure. The Subcutaneous Pentylenetetrazole (Metrazol<sup>R</sup>) Seizure Threshold Test (sc Met) entailed the administration of 85 mg/kg of pentylenetetrazole as a 0.5% solution subcutaneously in the posterior midline. This amount of pentylenetetrazole was expected to produce seizures in greater than 95% of mice. The animal was observed for 30 minutes. Protection was defined as a failure to observe even a threshold seizure (a single episode of clonic spasms of at least 5 sec duration). The results of these tests are tabulated in Table I.

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TABLE I

Comparative Median Effective Dosage

	Compound	Tox TD50 mg/kg	MES ED50 mg/kg	sc Met ED50 mg/kg
5	N-acetyl-D,L-alanine-N'-benzylamide	454 (417-501) *	77 (67-89) *	≠
10	N-acetyl-D-alanine-N'-benzylamide	214 (148-262) *	55 (50-60) *	55 (43-67) *
	N-acetyl-L-alanine-N'-benzylamide	841 (691-594) *	548 (463-741) *	≠
15	N-acetyl-D,L-phenylglycine-N'-benzylamide	>> 40	32.1	≠
	N-acetyl-D-phenylglycine-N'-benzylamide	>> 80	26.4	≠
20	N-acetyl-L-phenylglycine-N'-benzylamide	100-300	> 300	≠
	D,L- $\alpha$ -acetamido-N-benzyl-3-thiopheneacetamide	> 100	87.80	≠
25	D,L- $\alpha$ -acetamido-N-benzyl-2-thiopheneacetamide	30-100	44.80	≠
	D,L- $\alpha$ -acetamido-N-benzyl-2-furanacetamide	40	10.33	≠
30	D,L- $\alpha$ -acetamido-N-benzyl-2-pyrroleacetamide	< 100	16.10	≠

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TABLE I - cont'd.

Comparative Median Effective Dosage

	<u>Compound</u>	<u>Tox</u> <u>TD50 mg/kg</u>	<u>MES</u> <u>ED50 mg/kg</u>	<u>sc Met</u> <u>ED50 mg/kg</u>
5	D,L-2-acetamido-N-benzyl-2-ethoxy-acetamide	> 112	62.01	≠
10	D,L-2-acetamido-N-benzyl-2-methoxy-acetamide	< 300	98.30	≠
	(D,L)-α-Acetamido-N-benzyl-2-(5-methylfuran)acetamide	75.4 <sup>xx</sup>	19.2 (16.4-23.8)*	≠
15	(D,L)-α-Acetamido-N-benzyl-2-benzofuran-acetamide	>100<300 <sup>xx</sup>	>100<300	≠
	(D,L)-α-Acetamido-N-benzyl-2-benzo[b]-thiophenacetamide	>100<300 <sup>xx</sup>	>100<300	≠
20	(D,L)-α-Acetamido-N-benzyl-2-(5-methylpyrrole)acetamide	x	36.5 (30.6-57.1)*	≠
	(D,L)-α-Acetamido-N-(2-fluorobenzyl)-2-furan-acetamide	x	40.0	≠
25	(D,L)-α-Acetamido-N-(3-fluorobenzyl)-2-furan-acetamide	135.6 (114.9-161.8) <sup>xx</sup>	13.3 (11.5-15.3)*	≠

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		Tox TD 50 mg/kg	MES ED 50 mg/kg	scMet ED 50 mg/kg
16	2-acetamido-N-benzyl-2-aminoacetamide	†	65.1 (56.2-75.3)	†
5	2-acetamido-N-benzyl-2-(1-Pyrrolyl) acetamide	†	80.2	†
	2-acetamido-N-benzyl-2-(1-imidazolyl) acetamide	†	>100	†
10	2-acetamido-N-benzyl-2-(N,N-dimethylamino)acetamide	†	45.3	†
	2-acetamido-N-benzyl-2-(4-morpholine)acetamide	†	>30, <100	†
15	2-acetamido-N-benzyl-2-(N,N,N-trimethylammonium)acetamide tetrafluoroborate	†	>100	†
	2-acetamido-N-benzyl-2-(N-anilino)acetamide	†	>300	†
20	2-acetamido-N-benzyl-2-(N-(3-pyrazolylamino))acetamide	†	~100	†
	2,2-diacetamido-N-benzylacetamide	†	>100, <300	†
25	2-acetamido-N-benzyl-2-trifluoroacetamidoacetamide	†	>300	†
	2-acetamido-N-benzyl-2-(N-hydroxyamino)acetamide	†	~100	†
	2-acetamido-N-benzyl-2-(N-methoxyamino)acetamide	46.0 <sup>xx</sup> (38.0-56.0)	6.2 (5.4-7.2)	†
30	2-acetamido-N-benzyl-2-(N-(N-methylhydroxyamino))acetamide	†	~30	†
	2-acetamido-N-benzyl-2-(N-(N,Q-dimethylhydroxyamino)acetamide	50.5 <sup>xx</sup> (40.4-59.9)	6.7 (5.7-7.7)	†
35	2-acetamido-N-benzyl-2-(N-isoxazolidino)acetamide	†	31.4 (26.7-37.8)	†

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1	2-acetamido-N-benzyl-2-(N <sup>2</sup> -phenylhydrazino)acetamide	†	~100	†
5	2-acetamido-N-benzyl-2-(N <sup>2</sup> -benzyloxycarbonylhydrazino)acetamide	†	55.6 (49.3-63.9)	†
	2-acetamido-N-benzyl-2-hydroxyacetamide	†	80.1 (70.6-91.0)	†
10	2-acetamido-N-benzyl-2-(1-Pyrazolyl) acetamide	†	16.5 (14.1-22.5)	†
	2-acetamido-N-benzyl-2-phenoxyacetamide	†	>100	†
15	2-acetamido-N-benzyl-2-(methylmercapto)acetamide	†	>100	†
	2-acetamido-N-benzyl-2-(ethylmercapto)acetamide	†	>30, <100	†
20	2-acetamido-N-benzyl-2-(S-thiophenoxy)acetamide	†	>300	†
	2-acetamido-N-benzyl-2-(ethylmercapto)acetamide-S-oxide (diastereomer A)	†	>100	†
25	2-acetamido-N-benzyl-2-(ethylmercapto)acetamide-S-oxide (diastereomers A + B)	†	>100	†
	2-acetamido-N-benzyl-2-(ethylsulfonyl)acetamide	†	>100	†

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1	(D,L)- $\alpha$ -Acetamido-N-(4-fluorobenzyl)-2-furanacetamide	144.4 (122.5-170.9) <sup>XX</sup>	12.7 (10.4-15.1)*	*
5	(D,L)- $\alpha$ -Acetamido-N-(2,5-difluorobenzyl)-2-furanacetamide	x	23.8 (20.2-28.4)*	*
	(D,L)- $\alpha$ -Acetamido-N-(2,6-difluorobenzyl)-2-furanacetamide	x	>25<100	*
10	(D)-(-)- $\alpha$ -Acetamido-N-benzyl-2-furanacetamide	23.8 <sup>XX</sup>	3.3 (2.8-3.9)*	*
	(L)-(+)- $\alpha$ -Acetamido-N-benzyl-2-furanacetamide	>300	>100<300	*
15	(D,L)-2-Acetamido-4-pentenoic acid-N-benzylamide	x	33.6	*
	2-acetamido-N-benzyl-2-(2-Pyridyl) acetamide	†	8.5	†
20	(D,L)-2-Acetamido-N-benzyl-2-(methylamino)acetamide	95.0	44.5 (37.0-52.4)*	*
	(D,L)-2-Acetamido-N-benzyl-2-(ethylamino)acetamide	x	42.4 (37.2-47.8)*	†
25	(D,L)-2-Acetamido-N-benzyl-3-indoleacetamide	x	xxx	≠
	phenytoin	66	10	not effective
30	phenobarbital	69	22	13
	mephentyoin	154	61.	31
	phenacetamide	421 (337-549)*	87 (74-100)*	116 (71-150)*

\* 95% confidence intervals.

For The TD50 for this substrate was not computed.

xx The TD50 value was determined using the horizontal screen test.

xxx No activity was noted at  $\leq 300$  mg/kg

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Other results from the pharmacological protocols  
are summarized in Tables II, III and IV.

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












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72050x

Table II: Selected Physical and Pharmacological Data in Mice for  $\alpha$ -Acetamido-N-benzyl-2-furanacetamide (2)-Derivatives.<sup>a</sup>

1	5	CMP#	Ra	Rb	Rc	$\begin{array}{c} \text{X} \\ \parallel \\ \text{CH}_3\text{CNH} - \text{C} - \text{C} - \text{NHR}_e \\   \quad \parallel \\ \text{R}_b \quad \text{Y} \end{array}$		mp <sup>b</sup>	MES <sup>c</sup> ED <sub>50</sub> mg/kg	Tox <sup>d</sup> TD <sub>50</sub> mg/kg	PI <sup>e</sup>
						X	Y				
		3a		H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	O	O	159-161	51.7 (44.4-59.9)	f	-
		3b		H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	O	O	130-132	89.8 (78.4-103.4)	f	-
10		4		CH <sub>3</sub>	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	O	O	-h	>300	f	-
		5		H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	S	O	78-80	18.4 (15.9-22.0)	f	-
		6		H	CH <sub>2</sub> C <sub>6</sub> H <sub>5</sub>	S	S	99-101	>100	f	-
15		7		H	CH <sub>2</sub> - 	O	O	172-174	-30	f	-
		8		H	CH <sub>2</sub> - 	O	O	168-170	>100	f	-
20		9		H	CH <sub>2</sub> - 	O	O	159-161	-30	f	-
		10		H	CH <sub>2</sub> - 	O	O	210-212	>100	f	-











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Table II continued

1	11		H	NHNH- 	O	O	226-228	>100	f	-
	12		H	CH <sub>2</sub> - 	O	O	188-190	127 (10.4-15.1)	144 (123-171)	11.3
5	(R)-12		H	CH <sub>2</sub> - 	O	O	205-207	3.5 (2.9-4.4)	14.4 (7.3-28.9)	4.1
	(R)-13		H	CH <sub>2</sub> - 	O	O	210-212	<10	f	-
	(R)-14		H	CH <sub>2</sub> - 	O	O	193-195	>10, <30	f	-
10	phenytoin <sup>f</sup>							95 (8.1-10.4)	65.5 <sup>i</sup> (52.5-72.1)	69
	phenobarbital <sup>f</sup>							21.8 (15.0-22.5)	69.0 <sup>i</sup> (62.8-72.9)	32
	valproate <sup>h</sup>							272 (247-338)	426 <sup>i</sup> (369-450)	1.6

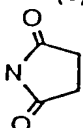
<sup>a</sup>The compounds were administered intraperitoneally. ED<sub>50</sub> and TD<sub>50</sub> values are in milligrams per kilogram. Numbers in parentheses are 95% confidence intervals. Time of peak effects in hours as determined in the Experimental Section is denoted in brackets. <sup>b</sup>Melting points (°C) are uncorrected. <sup>c</sup>MES = maximal electroshock seizure test. Compound was suspended in 30% PEG. <sup>d</sup>Tox = neurologic toxicity determined from horizontal screen unless otherwise noted. <sup>e</sup>PI = protective index (TD<sub>50</sub>/ED<sub>50</sub>). <sup>f</sup>Not determined. <sup>h</sup>Thick oil.

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T2070x

Table III Selected Physical and Pharmacological Data in Mice for N-Substituted  $\alpha,\alpha$ -Diamino Acid Derivatives.<sup>a</sup>

$$\text{CH}_3\overset{\text{O}}{\parallel}\text{CNH} - \overset{\text{R}^2}{\underset{|}{\text{CH}}} - \overset{\text{O}}{\parallel}\text{CNHCH}_2\text{Ph}$$

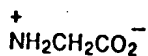
no	R <sup>2</sup>	mp <sup>b</sup>	MES <sup>c</sup> ED <sub>50</sub>	tox <sup>d</sup> TD <sub>50</sub>
2e	NHC(O)CH <sub>3</sub>	202-204	>30,<100	e
2f	NHC(O)OPh	201-203	>100	e
2g	NHC(O)NHCH <sub>3</sub>	229-230	>100	e
2h	NHC(O)NHPh	242-244	>100	e
2i	NHC(O)NHS(O <sub>2</sub> )Ph	188-191	>100	e
2j	NHC(S)NHCH <sub>3</sub>	162-163	>100	e
2k	NHC(S)NHPh	196-197	>100	e
2l	NHC(O)Ph(2'-CO <sub>2</sub> H)	186-188	>100	e
2m		181-183	>100	e
2n	NHC(O)CH <sub>2</sub> NHC(O)OCH <sub>2</sub> Ph	177-179	>10,<30	e
2o	NHCH <sub>2</sub> C(O)OCH <sub>2</sub> CH <sub>3</sub>	125-127	>100	e
2p	NHCH <sub>2</sub> C(O)OCH <sub>2</sub> Ph	133-135	72	74

20x

Table III continued

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124-126

phenytoin

95  
(8.1-10.4)

65.5<sup>f</sup>  
(52.5-72.1)

5

phenobarbital

21.8  
(15.0-22.5)

69.0<sup>f</sup>  
(62.8-72.9)

valproate

272  
(247-338)

426<sup>f</sup>  
(369-450)

10

<sup>a</sup>The compounds were administered intraperitoneally. ED<sub>50</sub> and TD<sub>50</sub> values are in milligrams per kilogram. Numbers in parentheses are 95% confidence intervals. Time of peak effects in hours as determined in the Experimental Section is denoted in brackets. <sup>b</sup>Melting points (°C) are uncorrected. <sup>c</sup>MES = maximal electroshock seizure test. Compound was suspended in 30% PEG unless otherwise noted. <sup>d</sup>Tox = neurologic toxicity determined from horizontal screen unless otherwise noted. <sup>e</sup>Not determined. <sup>f</sup>Neurologic toxicity determined using the rotarod test.

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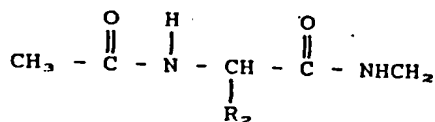
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Table IV Pharmacological Data in Mice for  $\alpha$ -Acetamido-N-Benzyl-2-Heterocyclic Derivatives



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




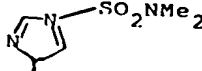



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$\text{R}_2$	MES <sup>a</sup> ED <sub>50</sub>	tox <sup>b</sup> TD <sub>50</sub>
	80.2	--
	16.5	66.9 (55.6-81.1)
	>100	--
	>30, <100	--
	>300	--
	>100	--
	>100	>100
	>100	--
	>100	--

<sup>a</sup> MES = maximal electroshock seizure test. Compound was suspended in 30% PEG.

<sup>b</sup> TOX = neurologic toxicity determined from horizontal screen unless otherwise noted.

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Thus, while the invention has been described with  
reference to certain preferred embodiments, those skilled in  
the art will realize that changes and modifications may be  
made thereto without departing from the full and intended  
5 scope of the appended claims.

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